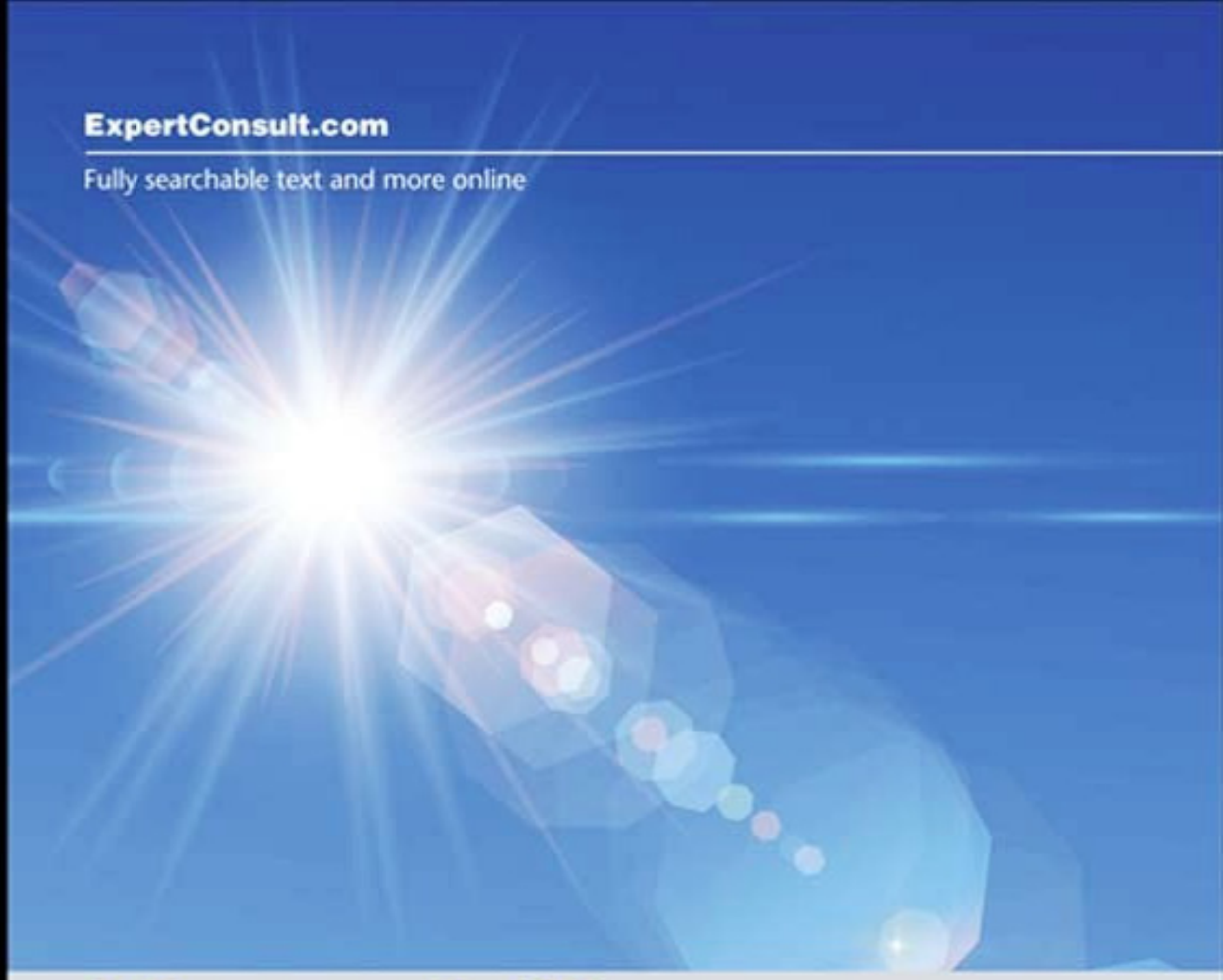

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A SYSTEMATIC APPROACH

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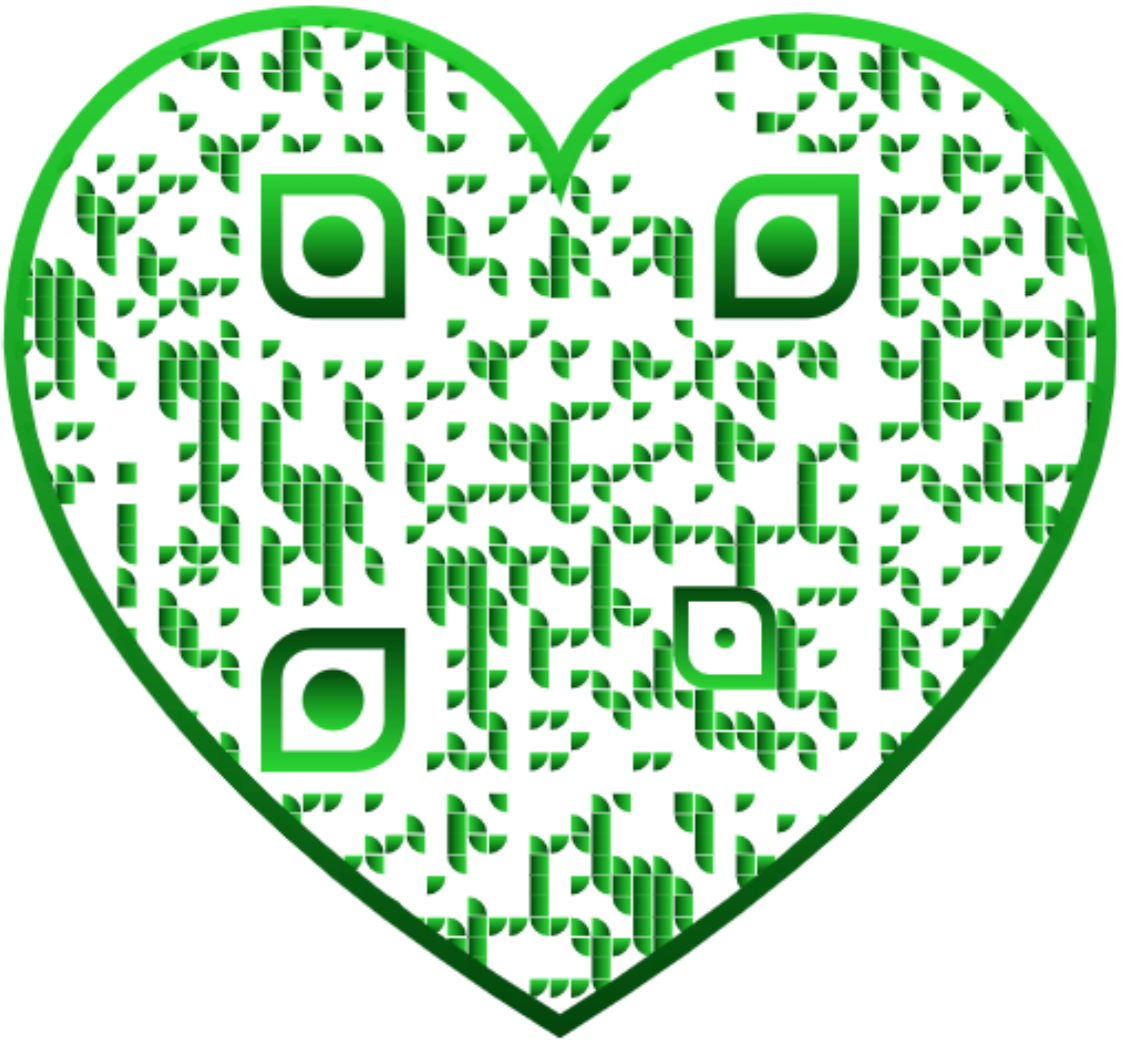
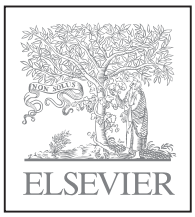


Kanski's Clinical Ophthalmology

A SYSTEMATIC APPROACH

EIGHTH EDITION

Brad Bowling
FRCSEd(Ophth), FRCOphth, FRANZCO
Ophthalmologist
Sydney
New South Wales
Australia



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BENIGN EPIBULBAR TUMOURS

Conjunctival naevus

Introduction

A conjunctival naevus is the most common melanocytic conjunctival tumour; the overall risk of malignant transformation is less than 1%. Treatment by excision is usually for cosmesis, but sometimes for irritation or a suspicion of malignancy. The histological appearance is similar to that of cutaneous naevi, but as there is no conjunctival dermis, subepithelial and stromal replace dermal in the nomenclature:

- **Compound** naevi are characterized by the presence of naevus cells at the epithelial–subepithelial junction and within the subepithelial stroma, often with epithelial inclusions such as cysts and goblet cells (Fig. 12.1A).
- **Subepithelial** lesions are confined subepithelially.
- **Junctional** naevi consist of nests of naevus cells at the epithelial–subepithelial junction (Fig. 12.1B). They are uncommon.

Clinical features

- **Symptoms.** The lesion is typically initially noticed in the first or second decade.
- **Signs**
  - A solitary slightly or moderately elevated pigmented or partially pigmented lesion of variable size, most frequently juxtalimbal; over half contain small cysts (Figs 12.1C and D).
  - Naevi are mobile over the underlying sclera.
  - The extent of pigmentation is variable; absence is relatively common (Fig. 12.1E).
  - The plica, fornix and caruncle (Fig. 12.1F) are uncommon locations.
  - Naevi may become inflamed, especially in children and adolescents, and this may be mistaken for malignant change.
- **Signs of potential malignancy**
  - An unusual site such as the palpebral or forniceal conjunctiva.
  - Prominent feeder vessels.
  - Sudden growth or increase in pigmentation.
  - Development after the second decade.

Conjunctival papilloma

Conjunctival papillomata are strongly associated with human papillomavirus infection, especially types 6 and 11. Histopathologically they consist of a fibrovascular core covered by an irregular proliferation of non-keratinized stratified squamous epithelium containing goblet cells (Fig. 12.2A).

Clinical features

Lesions are sessile (wide base and flattish profile – Figs 12.2B and C) or pedunculated (frond-like – Fig. 12.2D), and are frequently located in the juxtalimbal area, fornix or the caruncle. They are usually solitary but may be multiple.

Large lesions may cause irritation, interfere with lid closure or encroach onto the cornea.

Treatment

Small lesions may resolve spontaneously. Large lesions are treated by excision, sometimes with cryotherapy to the base and the surrounding area. Options for recurrences include subconjunctival interferon alfa, carbon dioxide laser vaporization, topical mitomycin C and oral cimetidine.

Limbal dermoid

A limbal dermoid is a choristoma (a mass of histologically normal tissue in an abnormal location) consisting of a mass of collagenous tissue containing dermal elements; it is covered by stratified squamous epithelium (Fig. 12.3A). Presentation is in early childhood, with a smooth, yellowish, soft subconjunctival mass commonly located at the inferotemporal limbus, often with protruding hair (Fig. 12.3B). Lesions are occasionally very large and may virtually encircle the limbus (Fig. 12.3C). Treatment is indicated for cosmesis, chronic irritation, dellen formation and amblyopia from astigmatism or involvement of the visual axis. Small dermoids can undergo simple excision, but lamellar keratosclerectomy may be required for large lesions.

Systemic associations

- **Goldenhar syndrome** (oculoauriculovertebral spectrum – Fig. 12.3D) is usually sporadic.
  - Systemic features include hypoplasia of the malar, maxillary and mandibular regions, macrostomia and microtia, preauricular and facial skin tags, hemivertebrae (usually cervical), mental handicap, cardiac, renal and central nervous system (CNS) anomalies.
  - Ocular features, apart from dermoids, include upper lid notching or coloboma, microphthalmos and disc coloboma.
- **Treacher Collins syndrome** (see Ch. 1).
- **Linear naevus sebaceus of Jadassohn.**
  - Systemic features include warty or scaly cutaneous lesions, infantile spasms, CNS anomalies and developmental delay.
  - Ocular features, apart from dermoids, include ptosis, cloudy cornea, lid colobomas, fundus colobomas and microphthalmos.

Dermolipoma

A dermolipoma is similar in composition to a solid dermoid but also contains fatty tissue. Presentation tends to be in adult life as a soft yellowish subconjunctival mass near the outer canthus (Fig. 12.4A). The surface is usually keratinized, and in common with a dermoid, may exhibit hairs. Occasionally the lesion may extend into the orbit or anteriorly towards the limbus. Treatment is generally avoided due to the possibility of complications such as

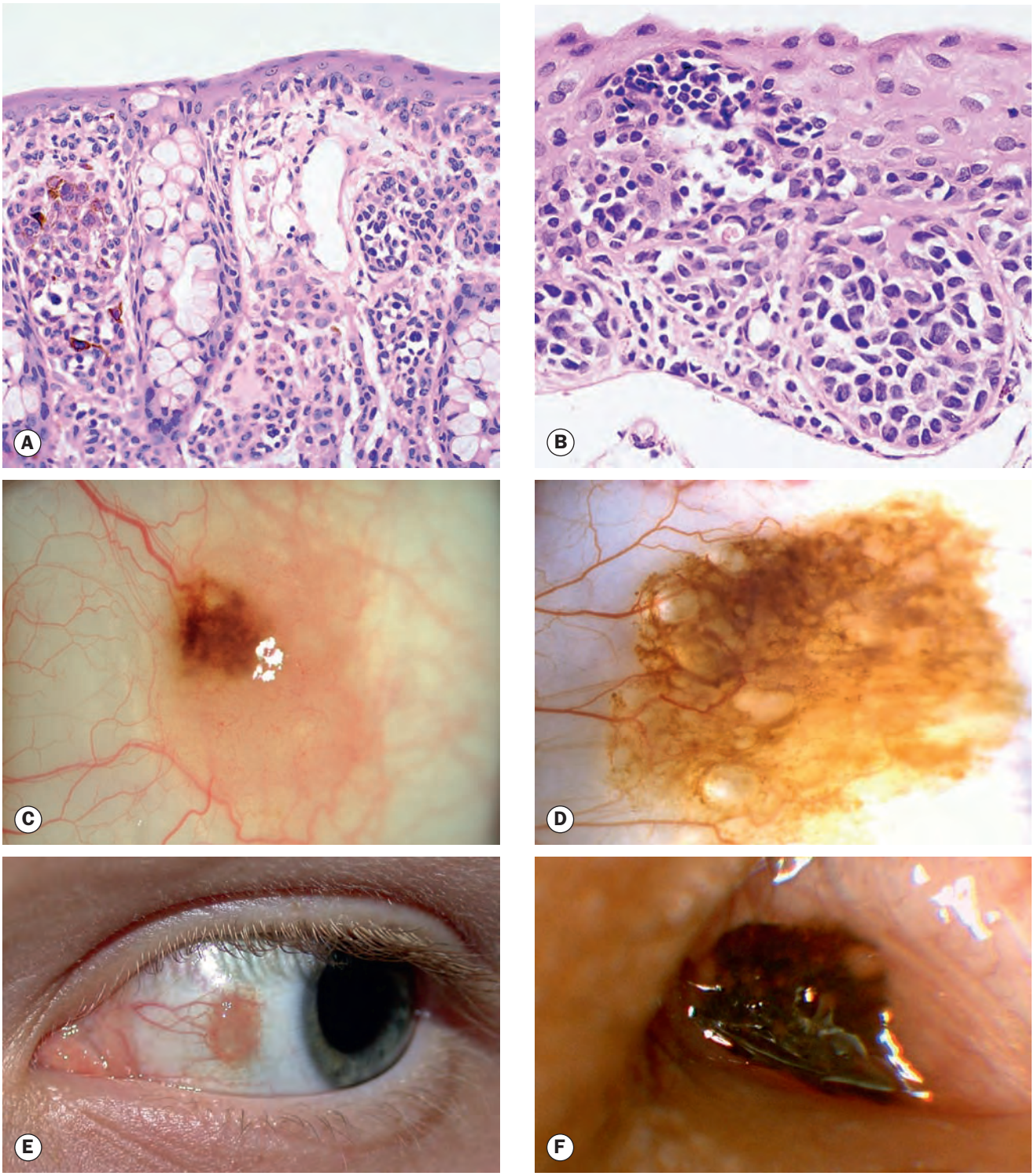

Fig. 12.1 Conjunctival naevus. **(A)** Compound naevus histology – see text; **(B)** junctional naevus histology – see text; **(C)** partially pigmented naevus; **(D)** cystic pigmented naevus; **(E)** non-pigmented naevus **(F)** caruncular location

(Courtesy of J Harry – fig. A; J Harry and G Misson, from Clinical Ophthalmic Pathology, *Butterworth-Heinemann 2001 – fig. B; S Chen – figs D and E)*

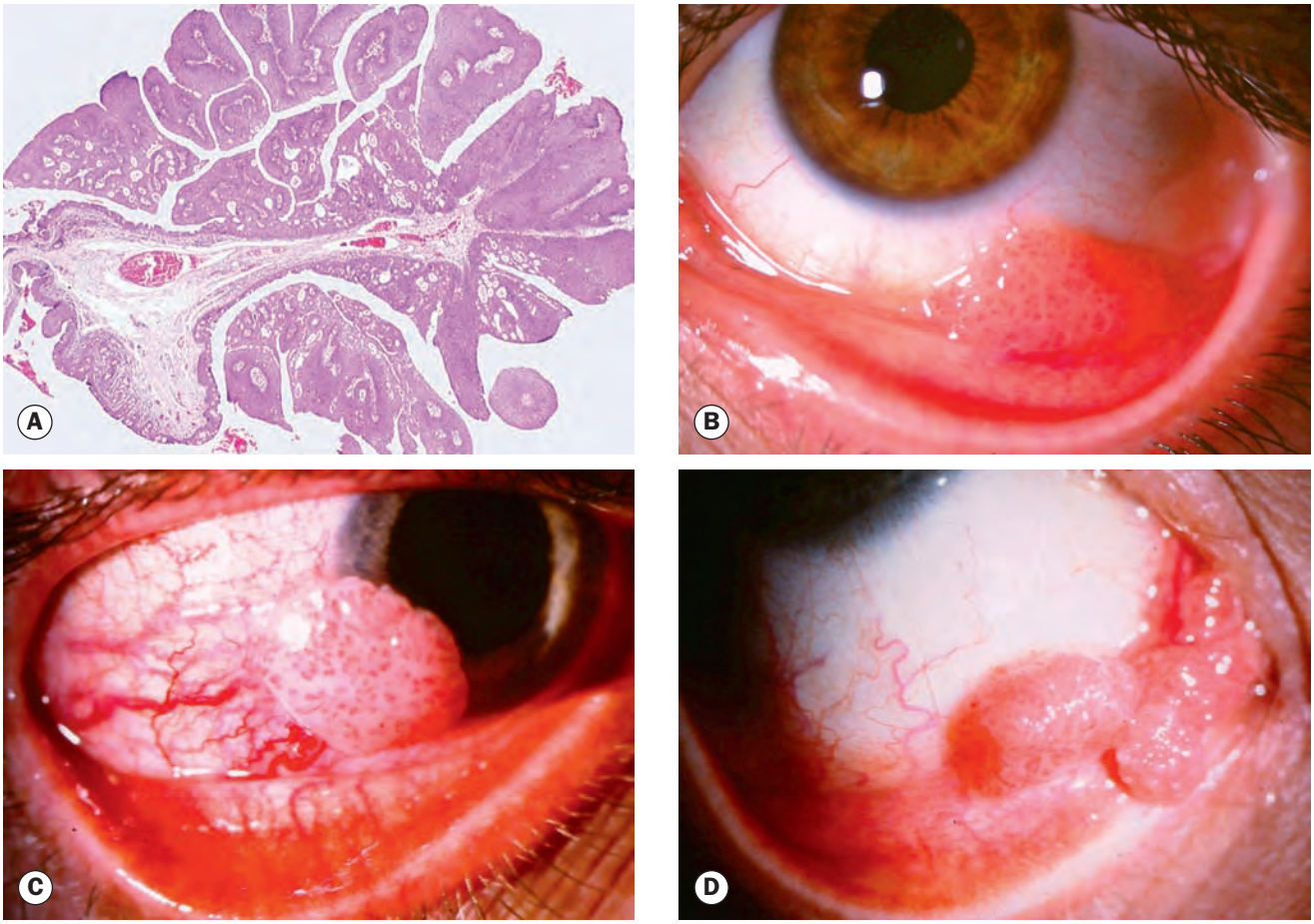

Fig. 12.2 Conjunctival papilloma. **(A)** Histology – see text; **(B)** sessile papilloma; **(C)** sessile papilloma with feeder vessels; **(D)** pedunculated papillomata
(Courtesy of J Harry – fig. A)

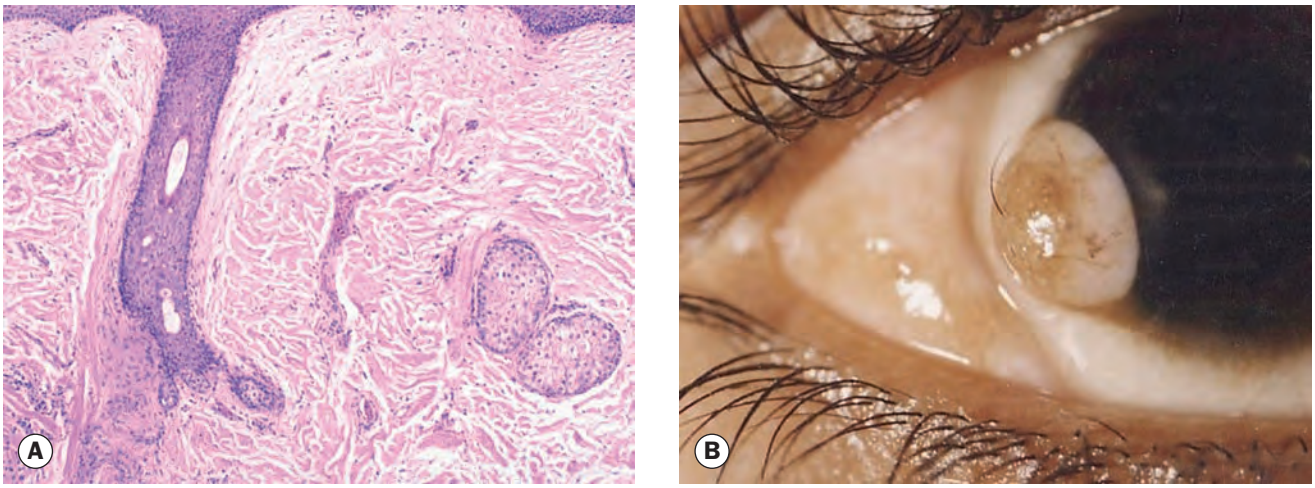

Fig. 12.3 Limbal dermoid. **(A)** Histology – see text; **(B)** typical lesion with protruding hair;

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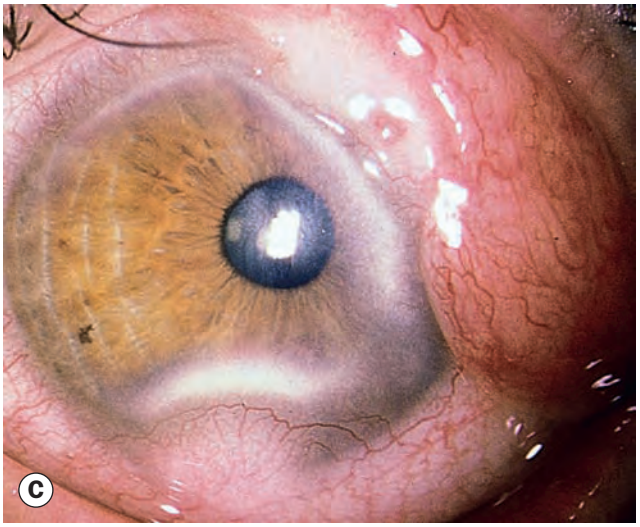
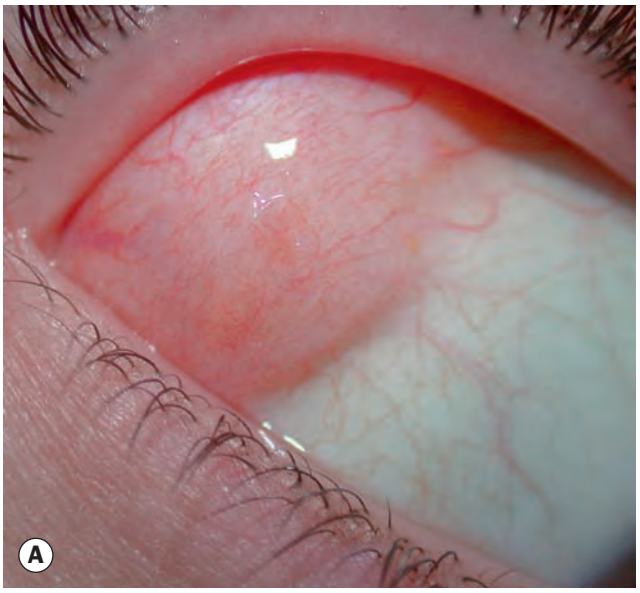


Fig. 12.3, Continued **(C)** complex dermoid; **(D)** Goldenhar syndrome
(Courtesy of J Harry and G Misson, from Clinical Ophthalmic Pathology, *Butterworth-Heinemann 2001 – fig. A; U Raina – fig. B)*



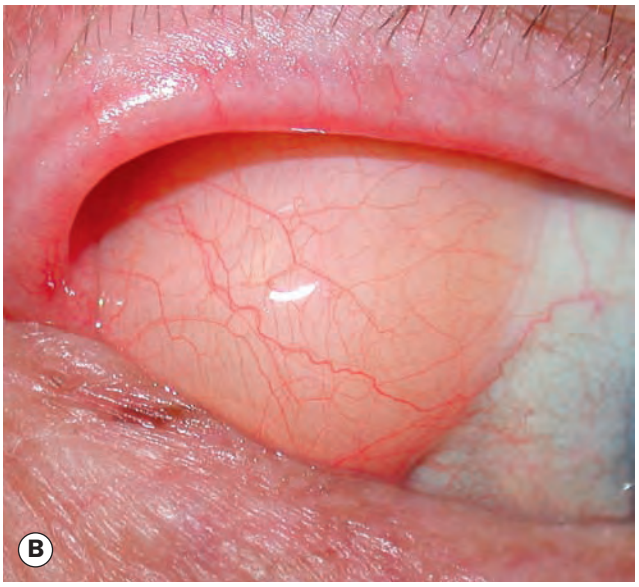


Fig. 12.4 **(A)** Dermolipoma; **(B)** orbital fat prolapse for comparison
(Courtesy of A Pearson)

scarring, ptosis, dry eye and ocular motility problems. In selected cases, debulking the anterior portion may improve cosmesis with lower risk. It is critical to distinguish a dermolipoma from a prominent lacrimal gland lobe and from orbital fat prolapse (Fig. 12.4B); lymphoma can also present in a similar fashion.

Pyogenic granuloma

A pyogenic granuloma is a fibrovascular proliferative response to a conjunctival insult such as surgery or trauma, or in association with a chalazion or foreign body incarceration. Histology shows granulation tissue with both acute and chronic inflammatory cells and a proliferation of small blood vessels; the term pyogenic granuloma is a misnomer as the lesion is neither pyogenic nor granulomatous. Presentation is typically a few weeks after surgery for chalazion, strabismus or enucleation, with a rapidly growing dark pink fleshy conjunctival mass (Fig. 12.5A). Treatment with topical steroids is often successful; resistant cases require excision. The differential diagnosis includes suture granuloma, which can often be large and mistaken for a malignant lesion (Fig. 12.5B) and Tenon capsule granuloma or cyst.

Miscellaneous benign epibulbar tumours

- **Epibulbar telangiectasia** (Fig. 12.6A) may be associated with Sturge–Weber syndrome.

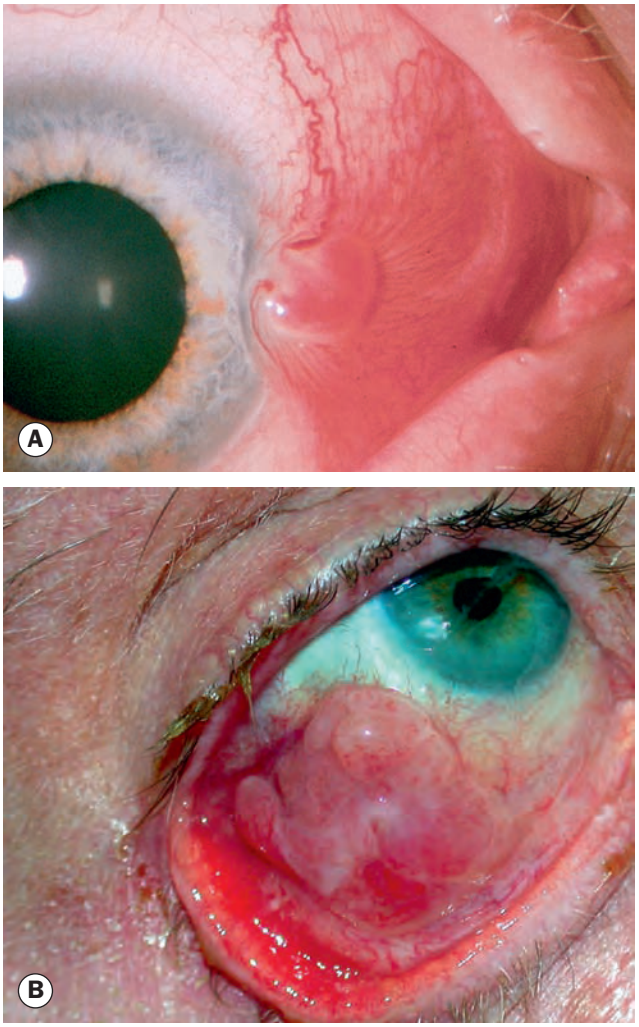


Fig. 12.5 **(A)** Pyogenic granuloma; **(B)** suture granuloma
(Courtesy of R Curtis – fig. A; Courtesy of S Chen – fig. B)

- **Reactive pseudoepitheliomatous hyperplasia** is a rapidly growing white juxtalimbal hyperkeratotic nodule (Fig. 12.6B) that develops secondary to irritation.
- **Melanocytoma** is a rare congenital lesion. It manifests as a slowly enlarging black lump (Fig. 12.6C) that cannot be moved freely over the globe.

Benign melanosis

Benign conjunctival epithelial melanosis (conjunctival hypermelanosis) is a normal variant, more common in darker-skinned individuals (over 90% of blacks, 5% of whites) due to the presence of excess melanin within basal layer conjunctival epithelial melanocytes. Melanocyte numbers are normal, that is, there is no melanocytic hyperplasia. It may have a protective effect against neoplasia. Benign melanosis appears during the first few years of life, and becomes static by early adulthood; both eyes are affected but involvement may be asymmetrical. Areas of flat, patchy, brownish pigmentation may be seen throughout the conjunctiva but are often concentrated at the limbus (Fig. 12.7A) and around

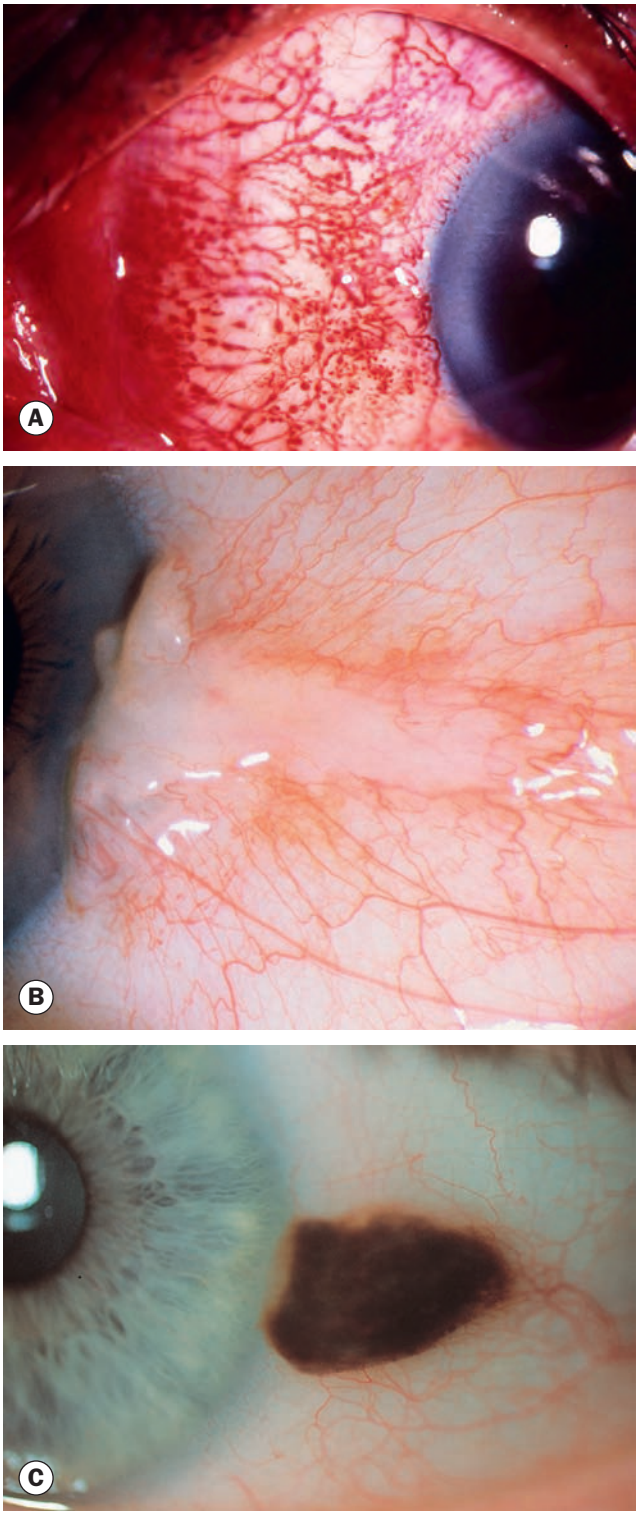


Fig. 12.6 Miscellaneous benign conjunctival tumours.
(A) Epibulbar telangiectasia in Sturge–Weber syndrome;
(B) reactive pseudoepitheliomatous hyperplasia;
(C) melanocytoma

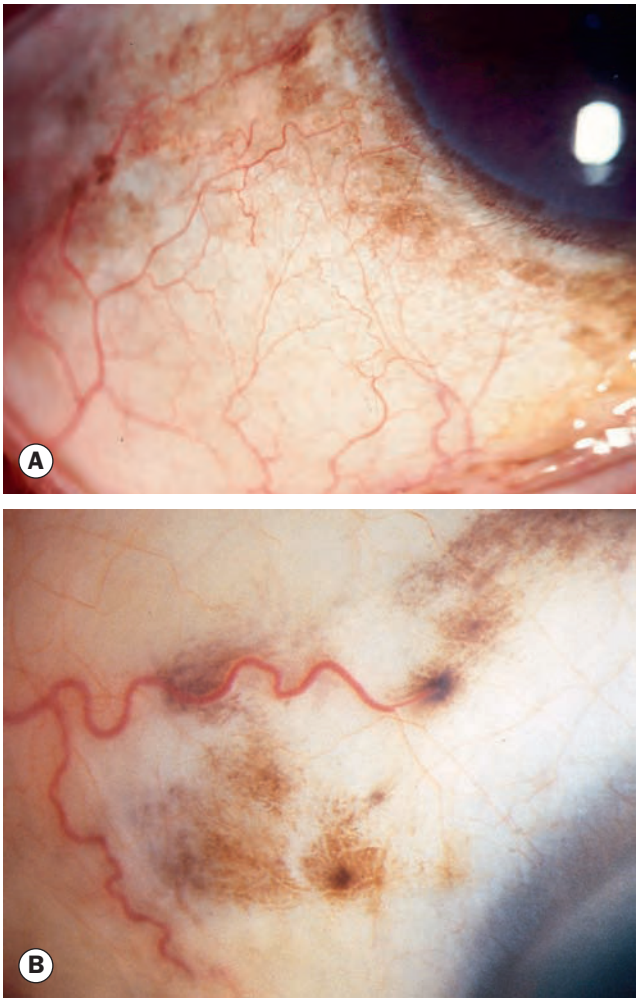


Fig. 12.7 Epithelial (racial) melanosis. **(A)** Juxtalimbal involvement; **(B)** at site of perforating vessel and nerve

perforating branches of vessels or nerves as they enter the sclera (Fig. 12.7B). The pigmented epithelium moves freely over the surface of the globe. A variant is seen in which small cysts are present.

MALIGNANT AND PREMALIGNANT EPIBULBAR TUMOURS

Primary acquired melanosis/ conjunctival melanocytic intra-epithelial neoplasia

Introduction

Approximately 75% of conjunctival melanomas (see below) arise in areas of melanocytic hyperplasia. Recent trends in the description of pigmented conjunctival lesions have led to controversy relating to terminology. Some classifications have historically used the term primary acquired melanosis (PAM) to encompass both benign epithelial melanosis (see above) and melanocytosis/ melanocytic hyperplasia (with and without atypia), whilst others have restricted its use to the latter category. To avoid this ambiguity, the term conjunctival melanocytic intra-epithelial neoplasia (C-MIN) may be preferred for lesions exhibiting proliferation of melanocytes, with PAM reserved for clinical description before a histological diagnosis has been established. The differential diagnosis includes conjunctival naevus, benign melanosis, congenital ocular melanocytosis (see below), secondary pigmentation in Addison disease and pigmented squamous cell carcinoma.

- **PAM without cellular atypia or with mild atypia** is a benign intraepithelial proliferation of epithelial melanocytes (Fig. 12.8A) with little or no risk of malignant transformation.
- **PAM with severe atypia** can be regarded as melanoma *in situ* that has a substantial chance of progression to invasive melanoma over several years. The risk is higher the greater the extent of the lesion, measured in clock hours. Severe atypia is present in only a small minority of PAM.
- **C-MIN** is graded from 0 to 10 according to degree of atypia and spread, 0 corresponding to an absence of any melanocyte proliferation or atypia (i.e. melanosis only) and 5 to conjunctival melanoma *in situ*.

Diagnosis

- **Symptoms.** A pigmented area is noticed on the surface of one or both (10%) eyes at a median age of 56 years, usually in a white individual.
- **Signs**
  - Uni- or multifocal flat areas of irregular golden-brown to dark chocolate-coloured epithelial pigmentation, typically involving the limbus and interpalpebral region (Figs 12.8B and C). PAM *sine pigmento* has been reported.
  - Because any part of the conjunctiva may be affected, it is important to evert the eyelids (Fig. 12.8D); C-MIN may also extend onto the cornea.
  - Transformation to melanoma may be suggested by the appearance of nodular areas.
- **Investigation.** Careful documentation with drawing and/or photography of lesions undergoing observation is important. Immunohistochemical analysis of biopsied lesions is performed.
- **Treatment**
  - Observation of small (less than one clock hour) lesions may be appropriate; some advocate excision biopsy of every lesion.
  - Excision biopsy is generally preferred to incisional biopsy if possible (see under conjunctival melanoma below for surgical approach).
  - Double freeze–thaw cryotherapy may be administered to the excision site, and/or following histological confirmation of C-MIN postoperative topical mitomycin C, e.g. four cycles of 0.04% four times daily for 7 days separated by 3-week intervals, with punctum plugs *in situ* to reduce the risk of punctal stenosis and increase drug–surface contact time.

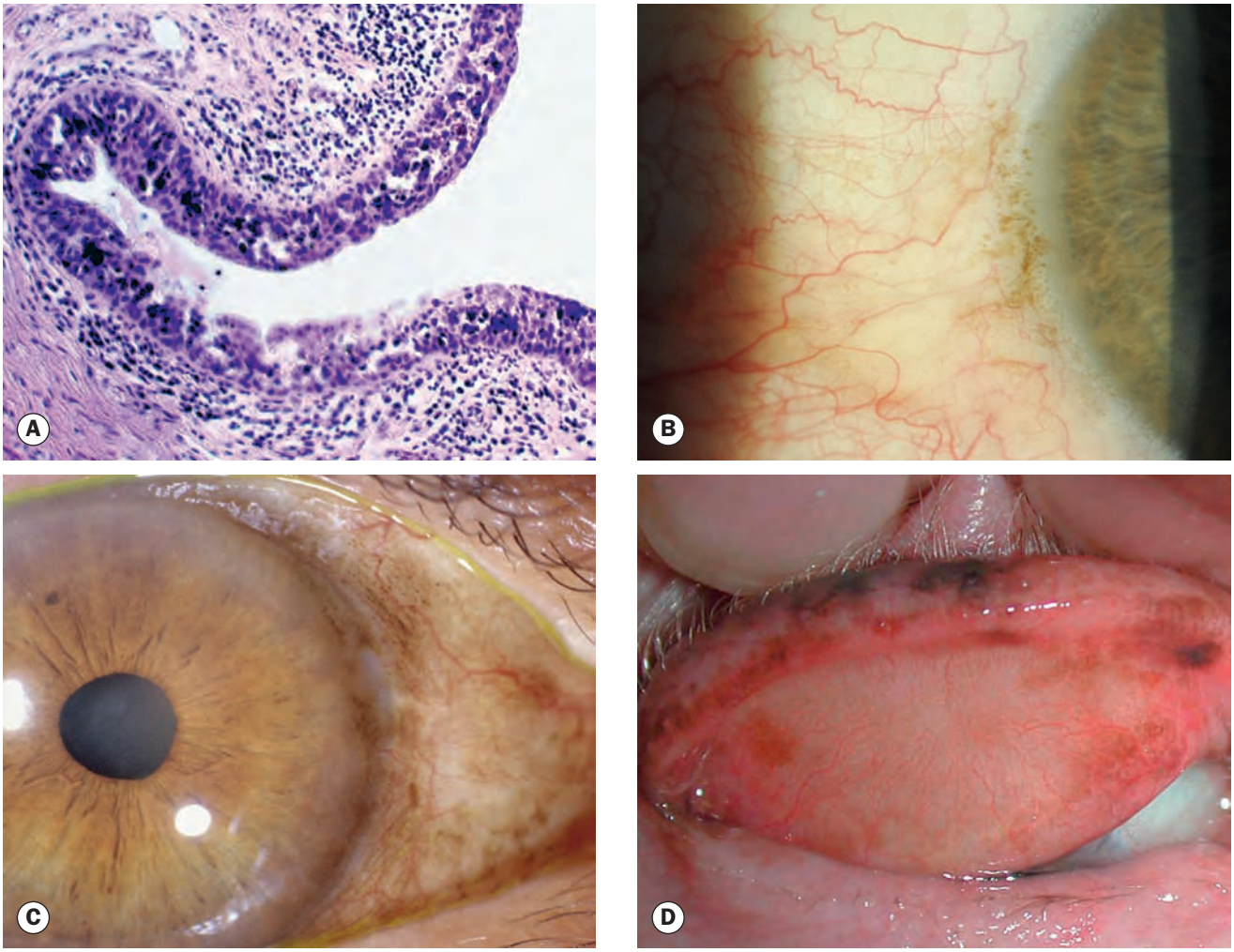


Fig. 12.8 Primary acquired melanosis (PAM). **(A)** Histology shows intraepithelial proliferation of conjunctival epithelial melanocytes; **(B)** small area of PAM; **(C)** more extensive PAM; **(D)** tarsal PAM associated with lentigo maligna of the eyelid
(Courtesy of J Harry and G Misson, from Clinical Ophthalmic Pathology, *Butterworth-Heinemann 2001 – fig. A; C Barry – fig. C; D Selva – fig. D)*

- Amniotic membrane grafting may be necessary for large excision sites.
- Larger lesions: mapping incisional biopsies can be accompanied by cryotherapy to all pigmented areas or topical mitomycin C as above.
- Long-term follow-up is mandatory in all cases.
- Corneal involvement: alcohol-mediated epitheliectomy followed by topical mitomycin C.

Conjunctival melanoma

Conjunctival melanoma is rare, accounting for about 2% of all ocular malignancies. Around 75% arise from an area of PAM, about 25% from a pre-existing junctional or compound naevus and rarely *de novo*. Presentation is often in the sixth decade, though patients with the rare dysplastic naevus syndrome develop multiple melanomas at a considerably younger age. The differential diagnosis includes naevus, ciliary body melanoma with extraocular extension, melanocytoma and pigmented conjunctival squamous carcinoma. The overall mortality is up to 19% at 5 years and 30% at 10 years. Metastasis occurs in 20–30%; the main sites are regional lymph nodes, lung, brain and liver. Factors associated with a worse prognosis include caruncular, forniceal or lid margin location and tumour thickness of 2 mm or more.

Diagnosis

- **Appearance.** A black or grey vascularized nodule that may be fixed to the episclera. The limbus is a common site, but a melanoma may arise anywhere in the conjunctiva (Fig. 12.9A). Association with PAM/C-MIN is very common (Fig. 12.9B).
- **Amelanotic tumours** may give rise to diagnostic difficulty (Fig. 12.9C).
- **B-scan ultrasonography** may be helpful in characterization of the lesion.
- **Systemic screening** consists of regular general examination, liver function testing and ultrasound, chest X-ray and possibly whole body positron emission tomography/computed tomography (PET/CT) imaging where available.
- **Histology** shows melanomatous cellular atypia with invasion of the subepithelial stroma (Fig. 12.9D).

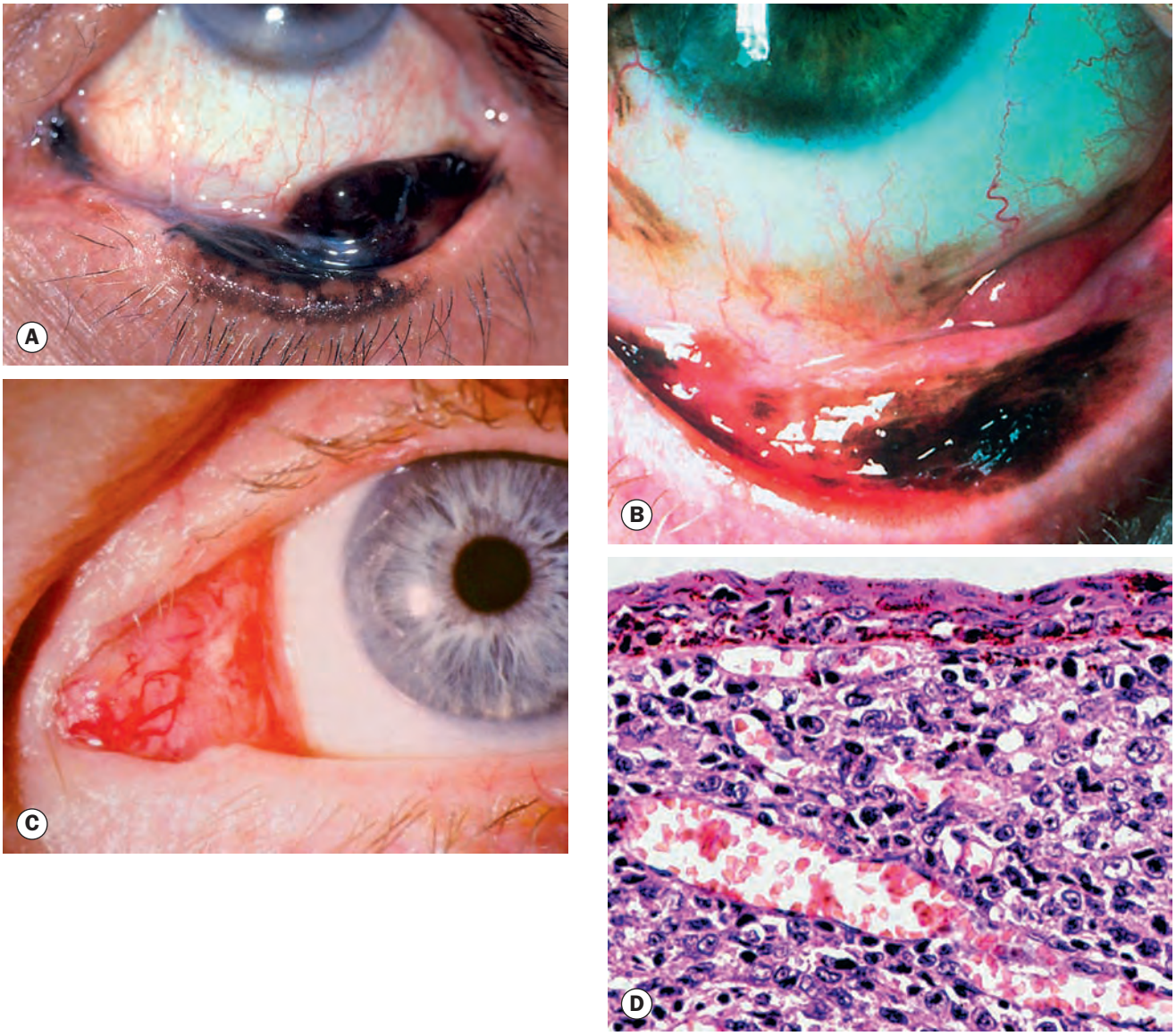


Fig. 12.9 Conjunctival melanoma. **(A)** Conjunctival melanoma extending into the eyelid; **(B)** multifocal melanoma arising from PAM; **(C)** amelanotic melanoma; **(D)** histology showing melanoma cells within the epithelium and subepithelial stroma
(Courtesy of C Barry – fig. A; J Harry – fig. D)

- **Sentinel lymph node biopsy** may be helpful in staging, though its place has not yet been fully defined.

Treatment

- Circumscribed lesions are treated by excision with a wide margin. As tumour seeding can occur during excision, contact with the tumour itself should be avoided and fresh instruments used to close the conjunctival defect.
- Adjunctive radiotherapy is routinely administered by some authorities, even if histology suggests that excision is complete; cryotherapy to the bed and surrounding tissue is an alternative. Proton beam radiotherapy can be applied if the caruncle or fornix is involved.
- Diffuse melanoma associated with extensive PAM/C-MIN is treated by excision of localized nodules with mitomycin C or cryotherapy to the diffuse component.
- Orbital recurrences are treated by local resection and radiotherapy. Exenteration may not improve survival and is therefore reserved for patients with extensive and aggressive disease when the eye cannot be preserved.
- The drug vemurafenib improves survival in patients with metastatic disease when the BRAF V600E mutation is present (50% of primary and metastatic conjunctival melanomas).
- Multifocal disease, non-limbal tumour location, tumour margin involvement and lack of adjunctive treatment are associated with a greater likelihood of recurrence.

Ocular surface squamous neoplasia

Introduction

Ocular surface squamous neoplasia (OSSN) describes a spectrum of benign, pre-malignant and malignant slowly progressive epithelial lesions of the conjunctiva and cornea. Older adults are usually affected unless a predisposing systemic condition is present. Risk factors include ultraviolet light exposure, a pale complexion, ciclosporin, smoking, petroleum product exposure, acquired immunodeficiency syndrome (AIDS) and xeroderma pigmentosum. Human papilloma virus infection (especially type 16) has been implicated in some cases. Metastatic disease is extremely rare.

Diagnosis

- **Symptoms.** A visible mass in one eye, sometimes accompanied by conjunctivitis-type symptoms.
- **Signs** are variable and clinical correlation with histological severity is unreliable. Most tend to develop within the interpalpebral fissure, particularly at the limbus, although any part of the conjunctiva or cornea may be involved. The lesion may appear fleshy, gelatinous, leukoplakic or papillomatous, superficial or feeder vessels may be prominent or the appearance may be avascular (Figs 12.10A–C). Intraocular extension is uncommon.
- **Investigations** include ultrasonic biomicroscopy (UBM) or anterior segment optical coherence tomography (OCT) to estimate the depth of invasion, exfoliative cytology and impression cytology.
- **Histology** shows the following spectrum; the first two are sometimes termed conjunctival–corneal intraepithelial neoplasia (CCIN):
  - Conjunctival epithelial dysplasia. Dysplastic cells are confined to the basal epithelial layers.
  - Carcinoma *in situ*. Dysplastic cells involve the full thickness of the epithelium.
  - Squamous cell carcinoma. Invasion of the underlying stroma (Fig. 12.10D).

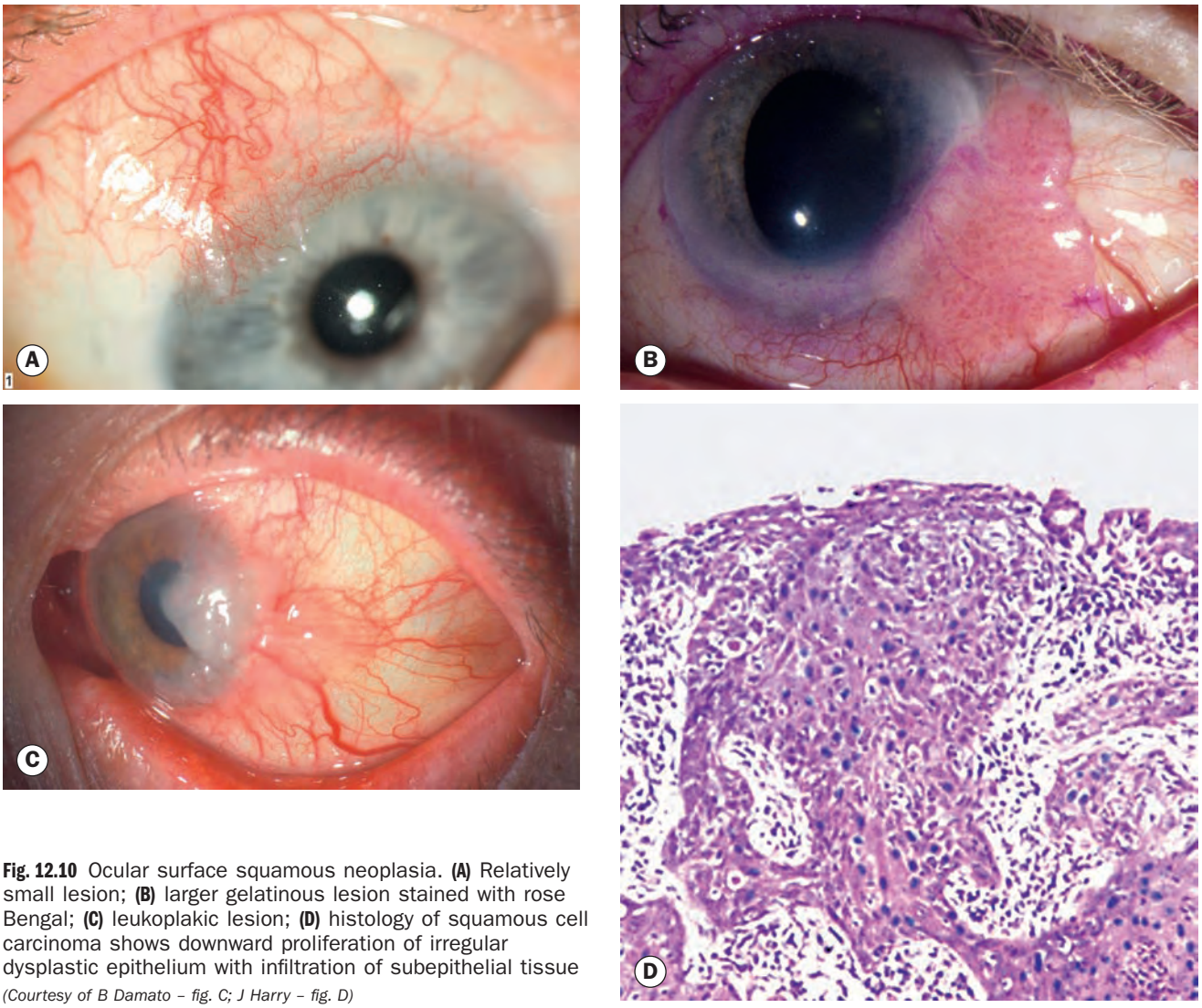


Fig. 12.10 Ocular surface squamous neoplasia. **(A)** Relatively small lesion; **(B)** larger gelatinous lesion stained with rose Bengal; **(C)** leukoplakic lesion; **(D)** histology of squamous cell carcinoma shows downward proliferation of irregular dysplastic epithelium with infiltration of subepithelial tissue
(Courtesy of B Damato – fig. C; J Harry – fig. D)

Treatment

- **Excision** with 2–4 mm margins and assessment for completeness of clearance, often with intraoperative frozen section, has been the conventional standard approach. Complete histological excision is associated with recurrence of 5–33%. Adjunctive measures reduce recurrence and include cryotherapy, brachytherapy or topical chemotherapy.
- **Topical chemotherapy.** Traditionally used as adjunctive treatment, this may also be employed as a primary modality to avoid the scarring and stem cell damage associated with extensive excision, to reduce tumour size prior to excision, or to treat recurrence. Agents include mitomycin C, 5-fluorouracil and interferon alfa-2b eye drop regimens; the latter two tend to be better tolerated.

Lymphoproliferative lesions

Introduction

The most common conjunctival lymphoproliferative lesion is reactive lymphoid hyperplasia, a proliferation of both B and T cells with germinal follicle formation. Conjunctival lymphoma may arise *de novo*, by extension from orbital lymphoma or associated with systemic lymphoma at diagnosis (up to 30%). Most conjunctival lymphomas are of B cell origin, arising from mucosa-associated lymphoid tissue (MALT) and tending to be indolent.

Diagnosis

- **Symptoms.** Painless swelling, redness or irritation; this is often bilateral, when systemic disease is more likely. Other possible symptoms include ptosis and diplopia.
- **Signs.** A slowly growing salmon-pink or flesh-coloured mobile infiltrate is seen on the epibulbar surface or in the fornices (Figs 12.11A and B). Rarely, a diffuse lesion may mimic chronic conjunctivitis.
- **Biopsy** is taken to confirm diagnosis; the uninvolved eye should also be biopsied (inferior fornix).
- **Investigation** for systemic involvement.

Treatment

- **Systemic disease** is treated as indicated, when local conjunctival measures may not be required.
- **External beam radiotherapy**.
- **Other options** include chemotherapy, excision of small lesions with adjuvant treatment, cryotherapy and intralesional injections of interferon alfa-2b or rituximab.

Kaposi sarcoma

Kaposi sarcoma is a slowly growing tumour that is typically found in patients with AIDS, but occasionally in the elderly and when there is long-term immunosuppression. A vascular bright red or purplish plaque or nodule is seen (Fig. 12.12), sometimes resembling (or associated with) conjunctival haemorrhage. Histology reveals a proliferation of spindle-shaped cells, vascular channels and inflammatory cells. If treatment is necessary, systemic AIDS therapy should be optimized, with local radiotherapy, excision and local or systemic chemotherapy as additional options.

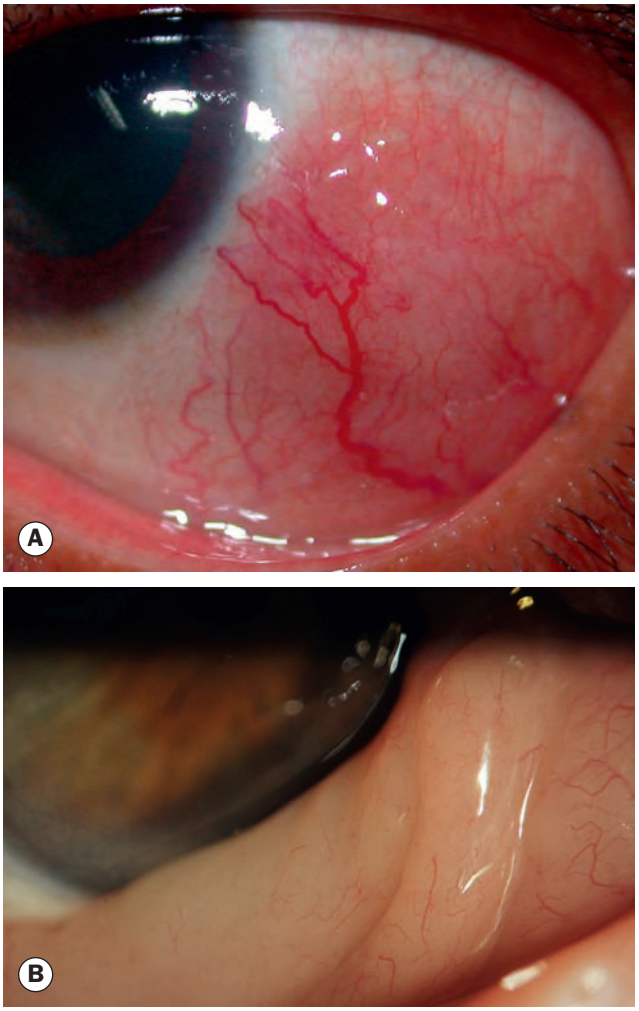


Fig. 12.11 Conjunctival lymphoproliferative lesions. **(A)** Epibulbar lymphoma; **(B)** large conjunctival lymphoma

IRIS TUMOURS

Iris naevus

Iris naevi consist of a proliferation of melanocytes in the superficial iris stroma, and appear as a circumscribed solitary flat or variably elevated pigmented lesion (Figs 12.13A–D). The normal iris architecture is disrupted. A diffuse naevus characteristically occurs in congenital ocular melanocytosis and in iris naevus (Cogan–Reese) syndrome (see Ch. 10). The malignant transformation rate

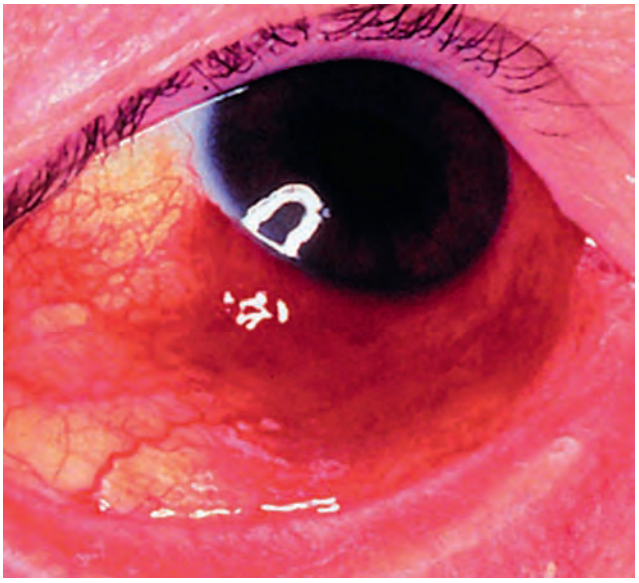


Fig. 12.12 Conjunctival Kaposi sarcoma

is up to 8% over 15 years; risk factors include young age (under 40), inferior location, bleeding from the lesion, diffuse iris involvement, feathery margins and ectropion uveae. Observation should be life-long and involve documentation by slit lamp examination and photography. Review should also include serial fundus examination, as iris naevus is a marker for all forms of uveal melanoma.

Iris freckle (ephelis)

Iris freckles (ephelides) are superficial lesions that are smaller than naevi, with no elevation or distortion (Fig. 12.14A and see Fig. 12.13A), and show increased melanocyte pigmentation but with a normal number of cells.

Brushfield spots

These are small whitish peripheral iris speckles arranged in a concentric ring (Fig. 12.14B), occurring particularly in Down syndrome though also as a normal finding in lighter irides. They consist of a focal mildly hyperplastic focus surrounded by a ring of hypoplasia and have no malignant potential (see also Ch. 9).

Lisch nodules

These are small well-defined nodules (Figs 12.14C and D) found in both eyes of virtually all patients with neurofibromatosis type 1 (see Ch. 19).

Fig. 12.13 Iris naevus. **(A)** Small lesion with mild ectropion uveae – freckles are also present; **(B)** larger naevus; **(C)** suspicious naevus with prominent associated vessels; **(D)** anterior chamber angle naevus

(Courtesy of C Barry – fig. B)

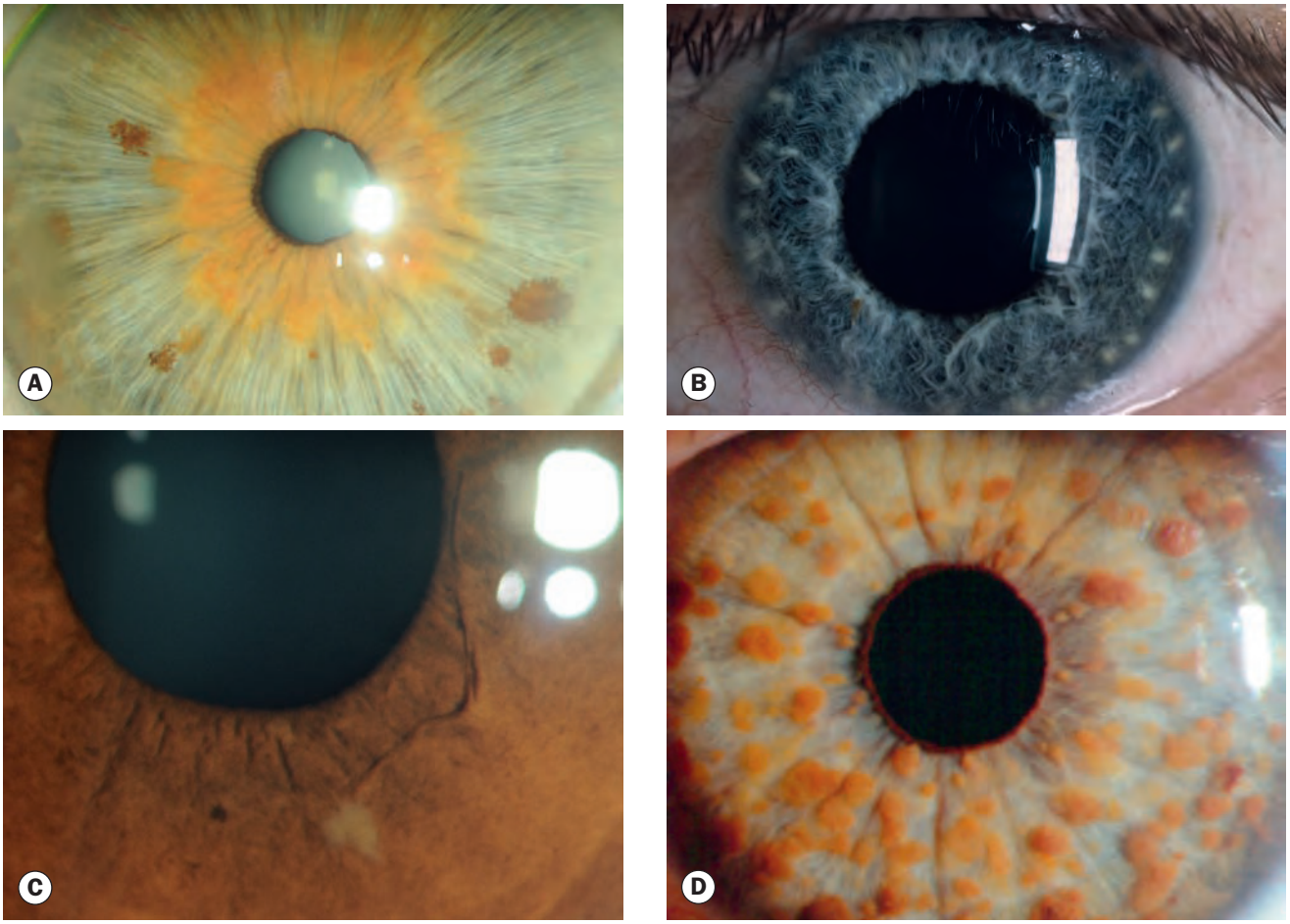


Fig 12.14 **(A)** Iris freckles; **(B)** Brushfield spots; **(C)** and **(D)** Lisch nodules in irides of different colours
(Courtesy of R Bates – fig. B)

Iris melanoma

Introduction

About 8% of uveal melanomas arise in the iris. The prognosis is comparatively good – only about 5% of patients develop metastasis within 10 years of treatment. Conditions associated with or predisposing to uveal melanomas include fair skin and lighter iris colour, numerous and/or atypical (dysplastic) cutaneous naevi, iris or choroidal naevi, congenital ocular and oculodermal melanocytosis (naevus of Ota) and uveal melanocytoma. Chronic sunlight exposure and arc welding are environmental risk factors. Presentation is typically in middle age, a decade earlier than ciliary body and choroidal melanoma.

Diagnosis

- **Symptoms.** Enlargement of a pre-existing naevus is typical, noticed either by the patient or at a routine eye examination. Signs indicative of malignant transformation include growth (Fig. 12.15) and the development of prominent blood vessels (see Fig. 12.13C).
- **Signs**
  - A pigmented (Fig. 12.16A) or non-pigmented (Fig. 12.16B) nodule at least 3 mm in diameter and 1 mm thick, typically located in the inferior half of the iris and often associated with surface blood vessels.
  - Pupillary distortion, ectropion uveae and occasionally localized cataract may be seen, although these can also occur with naevi.
  - Growth is usually slow, with extension across the iris surface.
  - The angle and anterior ciliary body may be infiltrated; extrascleral extension is rare (Fig. 12.16C).
  - Complications include hyphaema, cataract and glaucoma.
- **Histology** in the majority shows diffusely infiltrating spindle cells (see below) of low-grade malignancy (Fig. 12.16D). A minority contain an epithelioid cell component and can be more aggressive.
- **Ultrasound biomicroscopy** is used to rule out ciliary body involvement.
- **Fine-needle aspiration biopsy** may be employed prior to major surgical intervention.
- **Systemic investigation** should be carried out.

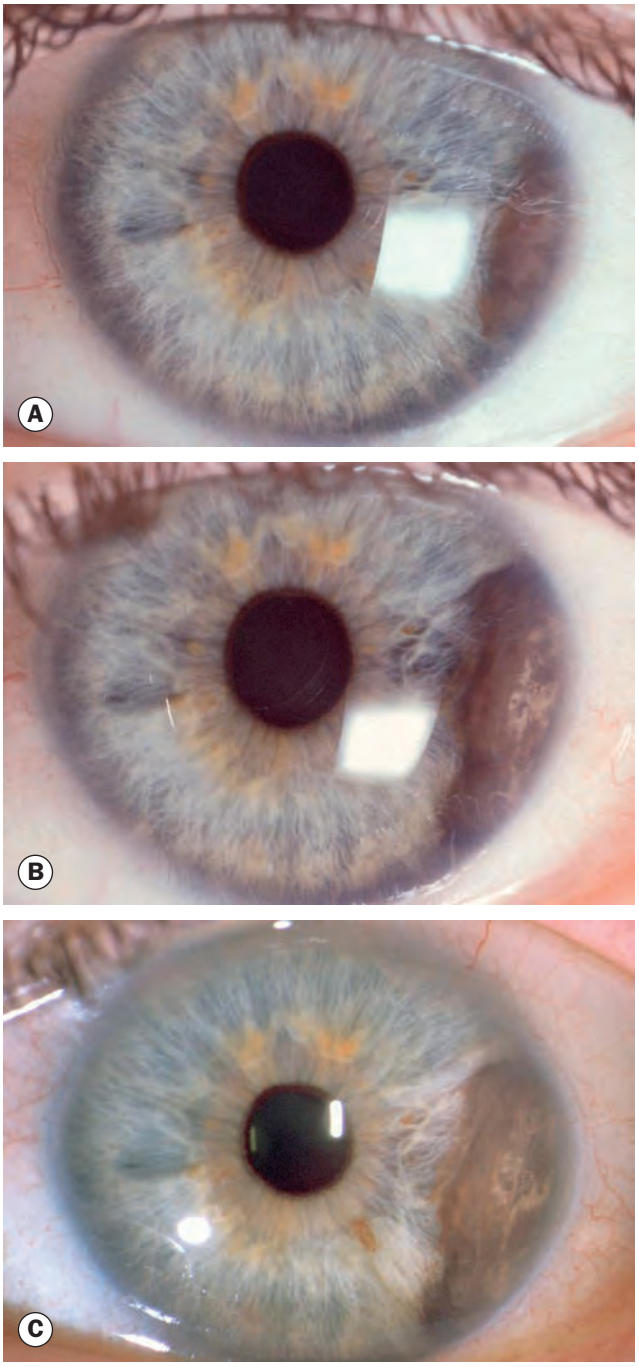


Fig. 12.15 Iris melanoma enlarging over several years
(Courtesy of C Barry)

Treatment

- **Sector iridectomy** for small tumours, and iridocyclectomy for tumours invading the angle.
- **Radiotherapy** with a radioactive plaque (brachytherapy) or external irradiation with a proton beam.
- **Enucleation** may be required for diffusely growing tumours, if radiotherapy is not possible.
- **Monitoring** for recurrence and metastasis.

Metastatic tumours

Metastasis to the iris (Figs 12.17A and B) is rare and is characterized by one or more fast-growing white, pink or yellow masses that may be associated with anterior uveitis and occasionally hyphaema. Breast and lung cancer and melanoma of the skin are among the most common types.

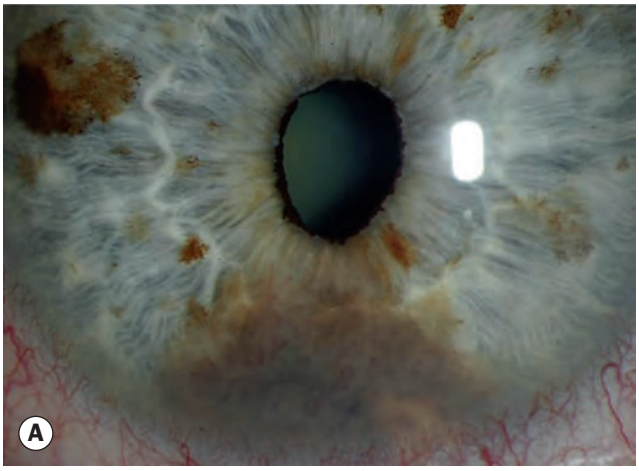
Miscellaneous iris tumours

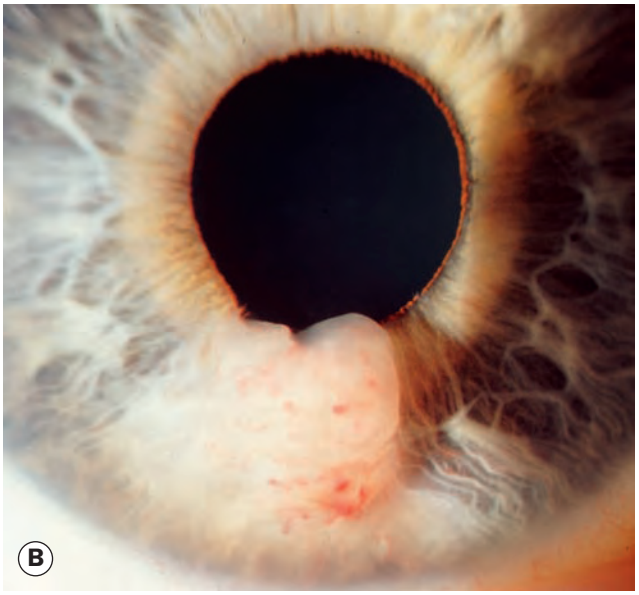
- **Juvenile xanthogranuloma** is a rare idiopathic granulomatous disease of early childhood that involves the skin, muscle, stomach, salivary glands and other organs. Iris involvement is characterized by a localized or diffuse yellow lesion (Fig. 12.18A) that may be associated with spontaneous hyphaema or, less commonly, anterior uveitis and glaucoma. Treatment is with topical steroids.
- **Leiomyoma** is an extremely rare benign tumour arising from smooth muscle. The appearance is similar to that of an amelanotic melanoma (Fig. 12.18B).
- **Melanocytoma** is a darkly pigmented nodular mass with a mossy, granular surface, most frequently occupying the peripheral iris (Fig. 12.18C). It may undergo spontaneous necrosis resulting in seeding of the iris stroma and chamber angle, with elevation of intraocular pressure.
- **Vascular tumours** of various types have been described, the most common being racemose haemangioma (arteriovenous communication), typically seen as a large ectatic vessel and/or bunch of grapes (Figs 12.18D and E).

IRIS CYSTS

Iris cysts are rare lesions. Anterior segment OCT and ultrasound biomicroscopy are especially useful to differentiate some lesions from ciliary body tumours.

- **Primary epithelial cysts**
  - Cysts arise from the iris or iridociliary pigment epithelium.
  - Three-quarters are in the peripheral iris, where they appear as a smooth dome-shaped bulging (Fig. 12.19A) best seen on gonioscopy (Fig. 12.19B). Mid-zone lesions again appear as a bulge in the iris – the wall may be manifest on pupillary dilatation. At the pupillary margin (least common), cysts appear darkly pigmented and often elongated.
  - They may rarely dislodge to float freely in the anterior chamber or vitreous (Fig. 12.19C).
  - The vast majority are asymptomatic and innocuous. Rarely, large cysts may obstruct vision and require collapse with photocoagulation.
- **Primary stromal cysts** may be congenital (more aggressive) or acquired.
  - Solitary unilateral structure with a smooth translucent anterior wall lying on or within the iris (Fig. 12.19D). Contained debris may be visible.
  - May remain stable for many years before enlarging; can sometimes rupture.





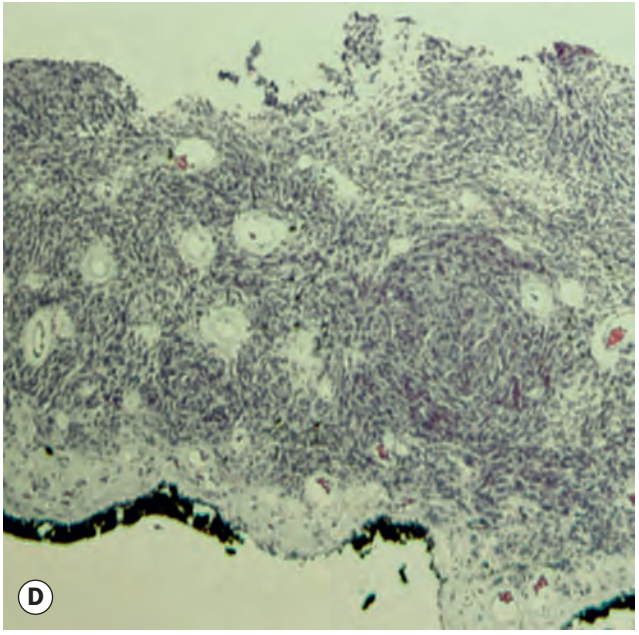


Fig. 12.16 Iris melanoma. **(A)** Typical iris melanoma; **(B)** amelanotic tumour; **(C)** angle invasion and extrascleral extension; **(D)** histology shows infiltration of the entire thickness of the stroma

(Courtesy of C Barry – figs A and C; J Harry and G Misson, from Clinical Ophthalmic Pathology, *Butterworth-Heinemann 2001 – fig. D)*

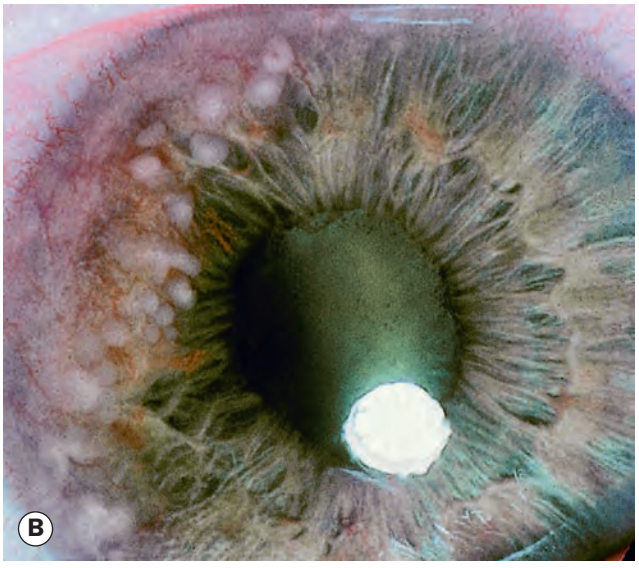


Fig. 12.17 Iris metastasis. **(A)** Metastasis from breast; **(B)** multiple small deposits

(Courtesy of P Saine – fig. A; B Damato – fig. B)

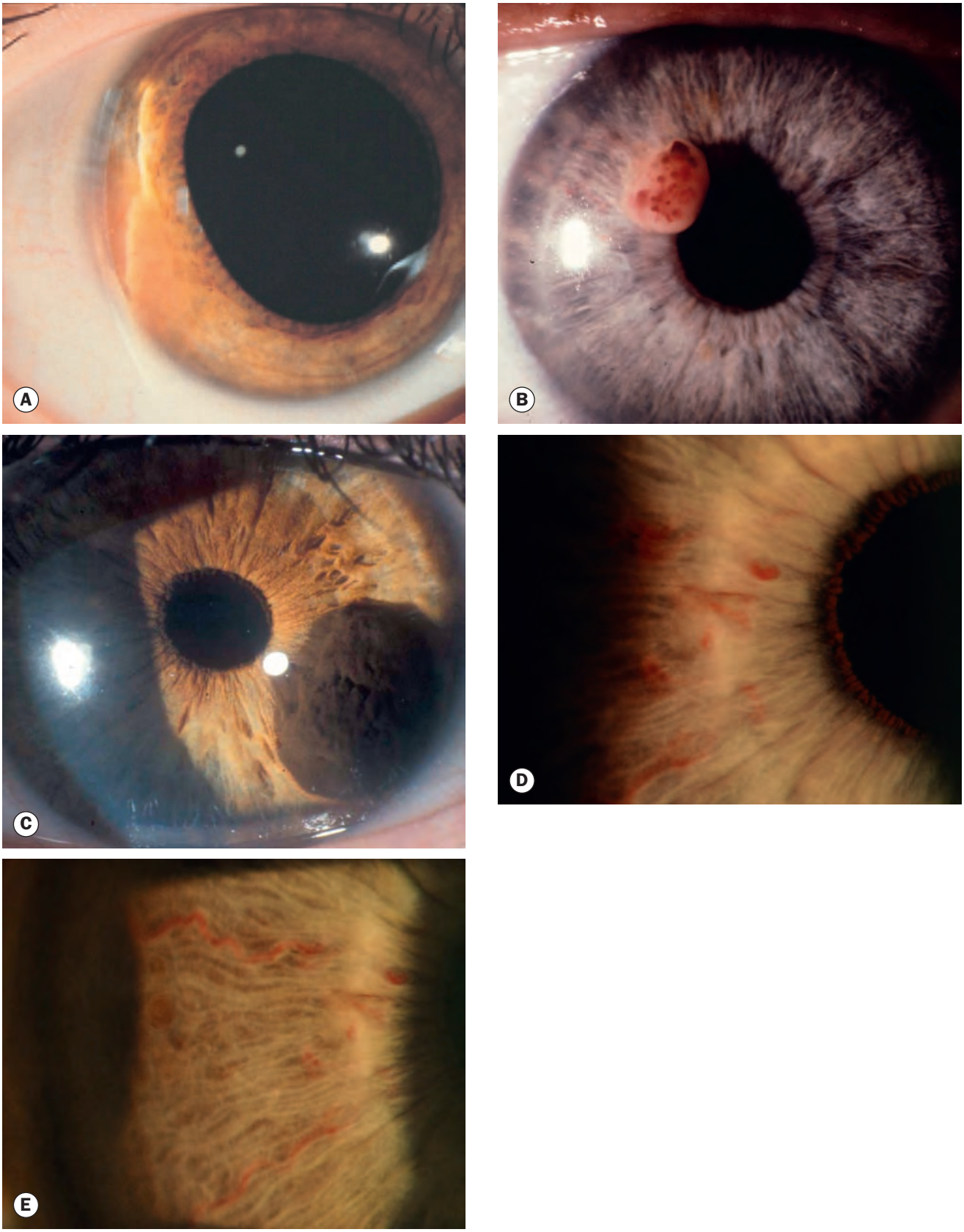


Fig. 12.18 **(A)** Juvenile iris xanthogranuloma; **(B)** leiomyoma; **(C)** melanocytoma; **(D)** racemose haemangioma; **(E)** supplying and draining vessels for lesion in **(D)**

(Courtesy of BJ Zitelli and HW Davis, from Atlas of Pediatric Physical Diagnosis*, Mosby 2002 – fig. A; B Damato – fig. B)*

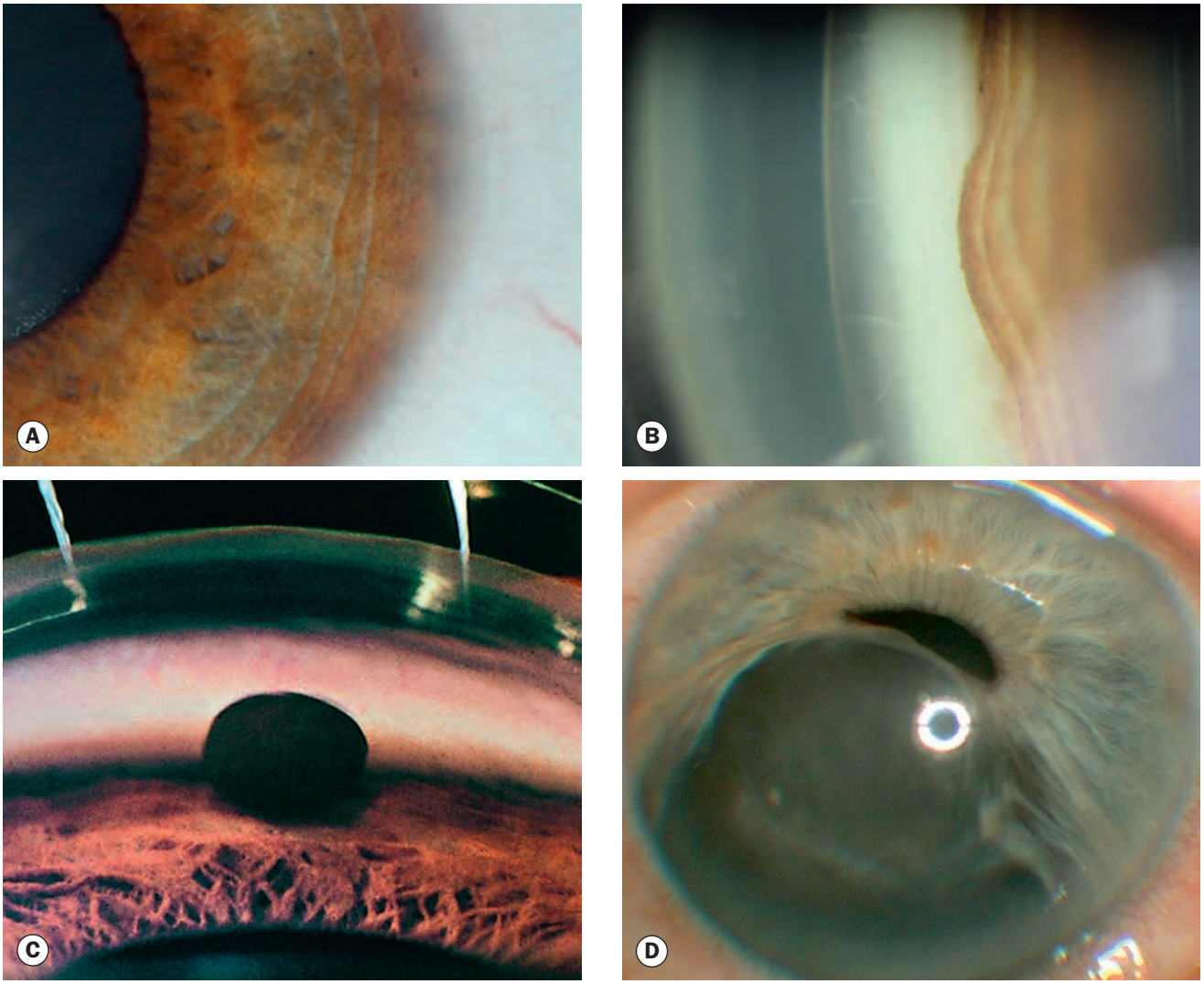


Fig. 12.19 Primary iris cysts. **(A)** Subtle dome-shaped elevation of the peripheral iris due to an epithelial cyst; **(B)** gonioscopy of lesion in **(A)**; **(C)** dislodged epithelial cyst in the angle; **(D)** very large stromal cyst
(Courtesy of Centre for Eye Health, Sydney – fig. A; J McAllister – fig. D)

- Most congenital cysts require treatment by aspiration or surgical excision. Ethanol-induced sclerosis may avoid the need for excision.

- **Secondary cysts**
  - Traumatic cysts (Fig. 12.20A) occur following deposition of epithelial cells from the conjunctiva or cornea onto the iris after penetrating or surgical trauma. They frequently enlarge, leading to corneal oedema, anterior uveitis and glaucoma.
  - Extended use of long-acting miotics may be associated with usually bilateral small, multiple cysts located along the pupillary border (Fig. 12.20B). Their development can be prevented by the concomitant use of topical phenylephrine 2.5%.
  - Parasitic cysts are extremely rare.

CILIARY BODY TUMOURS

Ciliary body melanoma

Introduction

Ciliary body melanomas comprise around 12% of all uveal melanomas. Risk factors are as for iris melanoma. Presentation is usually in the sixth decade with visual symptoms, although occasionally discovery is incidental; diagnosis may be delayed as the lesion is easily missed. Distinction is principally from an iridociliary cyst though uveal effusion syndrome may cause diagnostic difficulty that can be resolved by imaging. Other ciliary body tumours are extremely rare and include melanocytoma, medulloepithelioma,

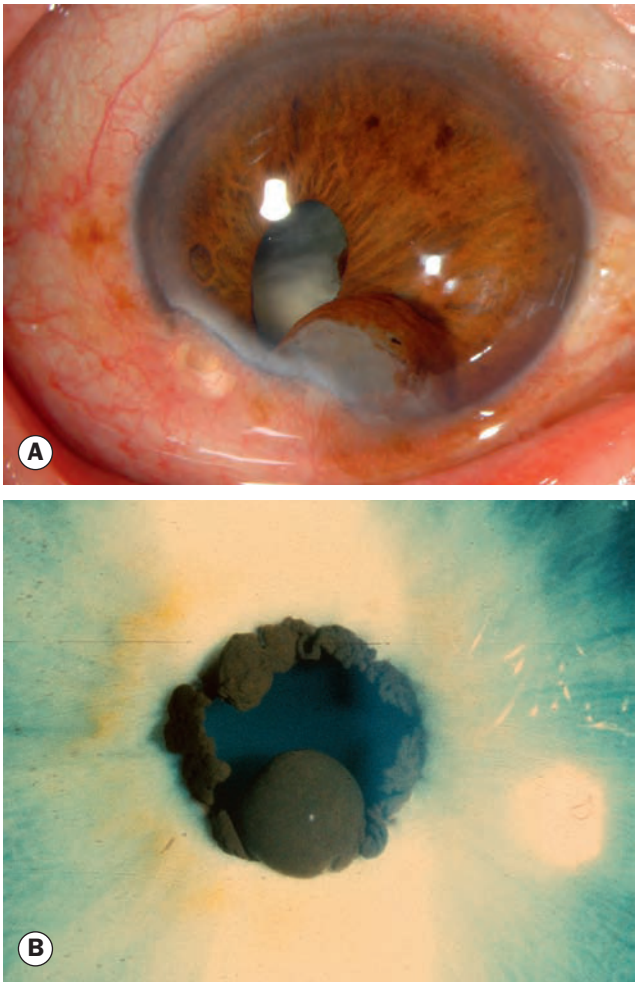


Fig. 12.20 Secondary iris cysts. **(A)** Traumatic cyst; **(B)** pupillary border cysts due to miotic therapy
(Courtesy of S Chen – fig. A; R Bates – fig. B)

metastases, adenocarcinoma, adenoma, neurolemmoma and leiomyoma.

Diagnosis

- **Signs**
  - A large tumour may be visualized with pupillary dilatation (Fig. 12.21A).
  - Overlying prominent episcleral (sentinel) vessels (Fig. 12.21B).
  - Erosion through the iris root may mimic iris melanoma, extraocular extension through scleral vessels a conjunctival melanoma (Fig. 12.21C).
  - Displacement of the lens (Fig. 12.21D) may cause astigmatism, subluxation or cataract.
- **Investigations**
  - Three-mirror contact lens examination and binocular indirect ophthalmoscopy.
  - Gonioscopy to detect angle invasion.
  - Ultrasonic biomicroscopy.
  - Biopsy involving excisional, incisional or fine-needle aspiration techniques may be helpful in selected cases. Genetic profiling may help to determine the likelihood of metastasis (see choroidal melanoma).
  - Investigation for systemic involvement, particularly hepatic.

Treatment

- **Iridocyclectomy** or sclerouvectomy for small or medium-sized tumours involving no more than one-third of the angle. Complications include retinal detachment, vitreous haemorrhage, cataract, lens subluxation, hypotony and incomplete resection.
- **Radiotherapy** by brachytherapy or proton beam irradiation.
- **Enucleation** may be necessary for large tumours.
- **Systemic treatment** is indicated when metastatic disease is evident.

Medulloepithelioma

Medulloepithelioma (previously known as diktyoma) is a rare embryonal neoplasm that arises from the inner layer of the optic cup and can be benign or malignant. Presentation is usually in the first decade with visual loss, pain, photophobia, leukocoria, or proptosis in advanced cases. A white, pink, yellow or brown ciliary body, retrolental or anterior chamber mass is seen (Figs 12.22A and B). Enucleation may be required.

TUMOURS OF THE CHOROID

Choroidal naevus

Choroidal naevi are present in 5–10% of Caucasians but are rare in darker-skinned races. Growth occurs mainly during the prepubertal years and is extremely rare in adulthood. For this reason clinically detectable growth should raise a suspicion of malignancy. The lifetime risk of malignant transformation is up to 1% from tertiary centre data. Histologically, the tumour is composed of a proliferation of spindle cell melanocytes within the choroid (Fig. 12.23A). It is vital to identify features suggesting a greater likelihood of malignancy; as with cutaneous melanoma, early treatment is associated with a substantially lower risk of metastasis. An extended period without any change provides no guarantee that progression will not occur in the future, as sudden enlargement of naevi has been documented following many years of stability.

Diagnosis

- **Symptoms**. The great majority are asymptomatic and detected on routine examination.
- **Signs**
  - Usually post-equatorial, oval or circular, brown to slate-grey lesion with indistinct feathery margins (Figs 12.23B and C).
  - Overlying drusen are typical.

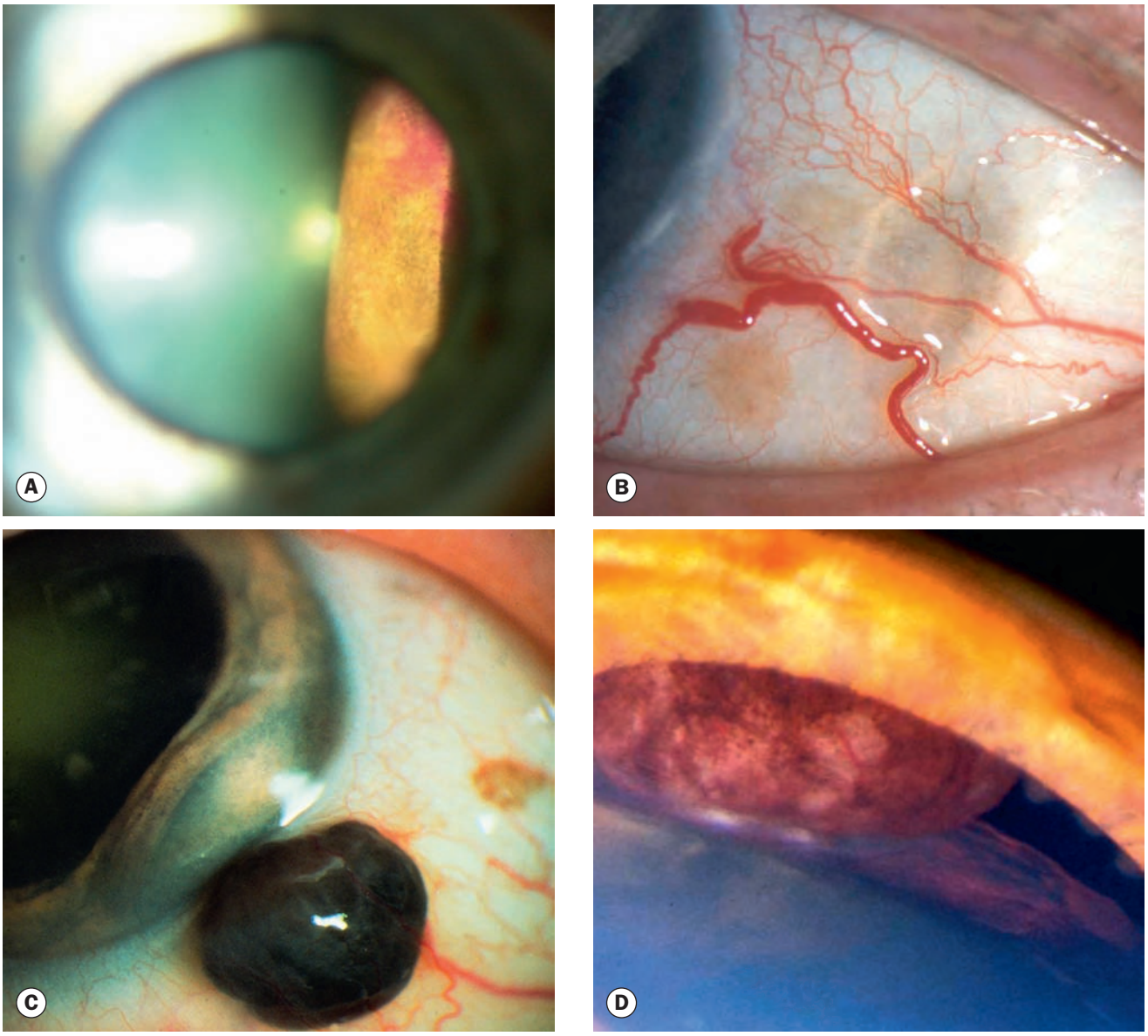


Fig. 12.21 Ciliary body melanoma. **(A)** Tumour seen on fundoscopy; **(B)** 'sentinel' vessels in the same quadrant as the tumour; **(C)** extraocular extension; **(D)** pressure on the lens
(Courtesy of B Damato – fig. B; R Curtis – fig. D)

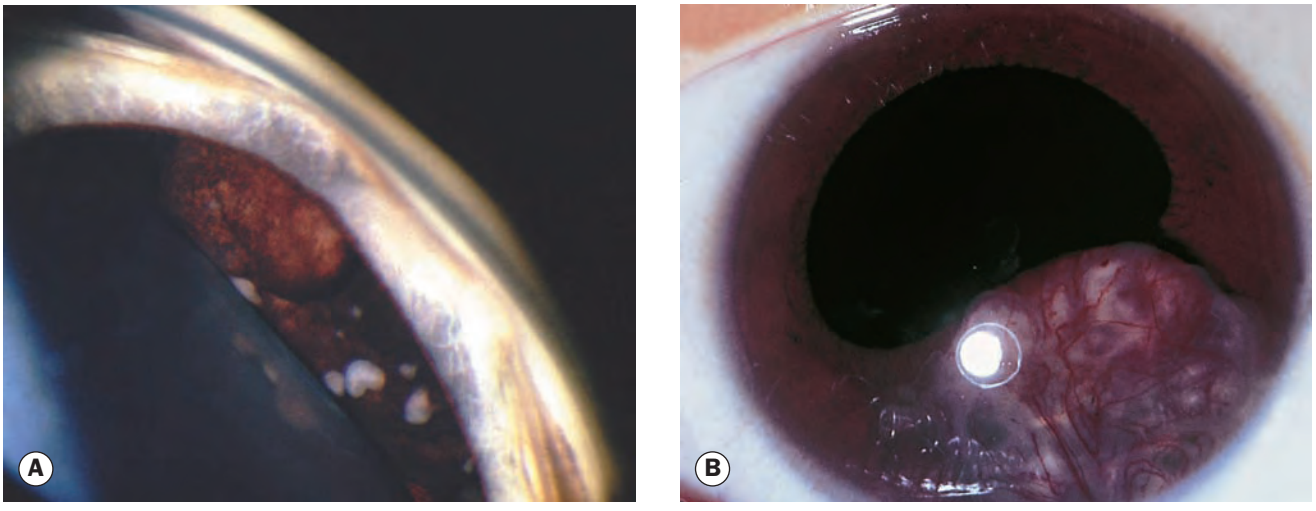


Fig. 12.22 Medulloepithelioma. **(A)** Cystic brown ciliary body mass; **(B)** anterior segment involvement
(Courtesy of R Curtis – fig. A)

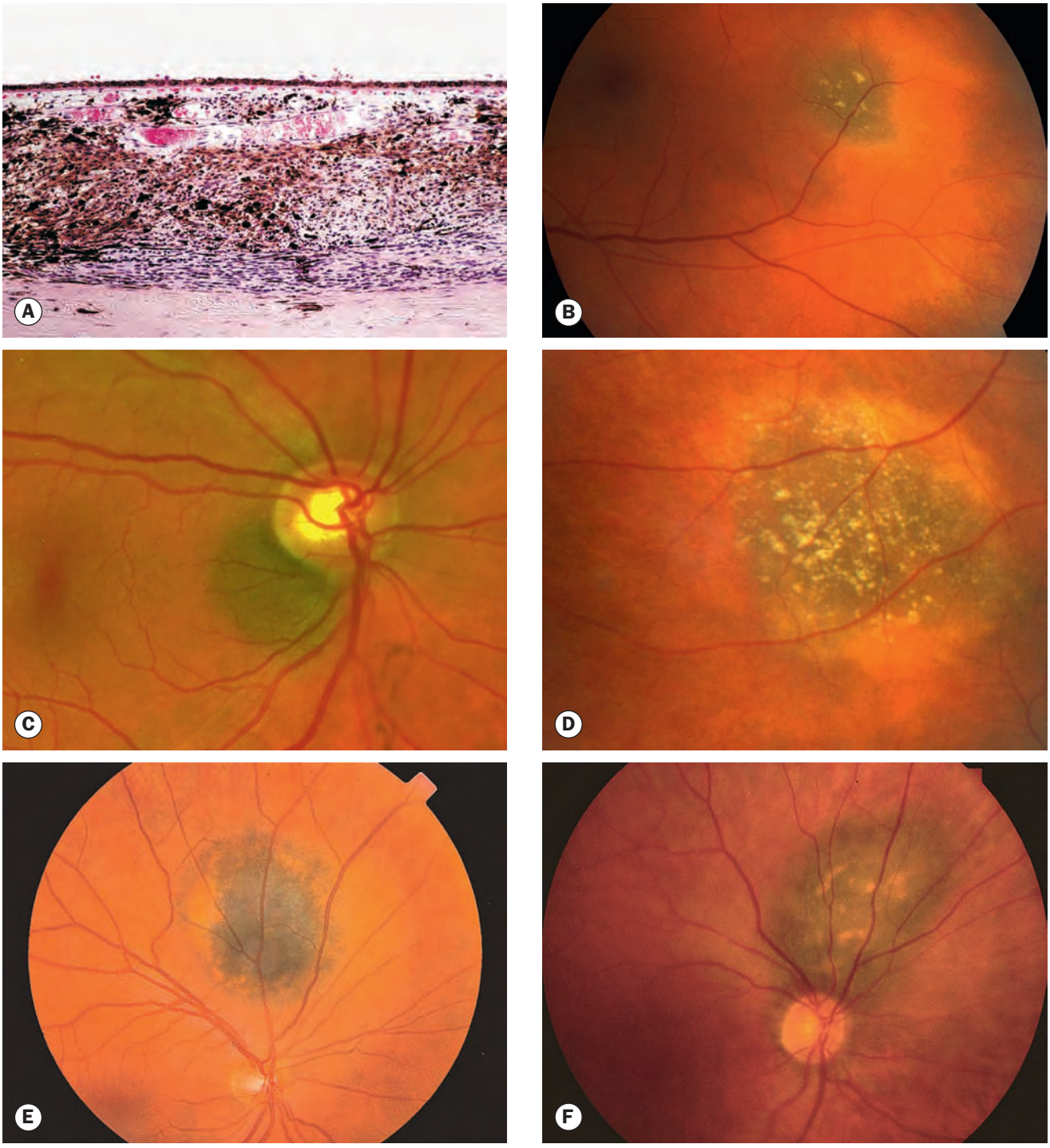


Fig. 12.23 Choroidal naevus. **(A)** Histology shows proliferation of melanocytes in the choroid, sparing the choriocapillaris; **(B)** typical small flat naevus with feathery edges, overlying drusen and a subtle broad halo; **(C)** peripapillary naevus; **(D)** naevus with overlying drusen and distinct halo; **(E)** and **(F)** overlying orange pigment

(Courtesy of J Harry – fig. A)

- A depigmented halo is very common (Fig. 12.23D).
- Amelanotic lesions can occur.

- **Features suspicious of early melanoma**
  - The presence of overlying orange pigment (lipofuscin – Figs 12.23E and F).
  - The presence of associated subretinal fluid.
  - Acoustic hollowness on ultrasonography (US).
  - Symptoms such as photopsia, blurred vision.
  - Thickness greater than 2 mm; diameter over 5 mm.
  - Absence of drusen.
  - Margin within 3 mm of the optic disc.
  - The absence of a halo.

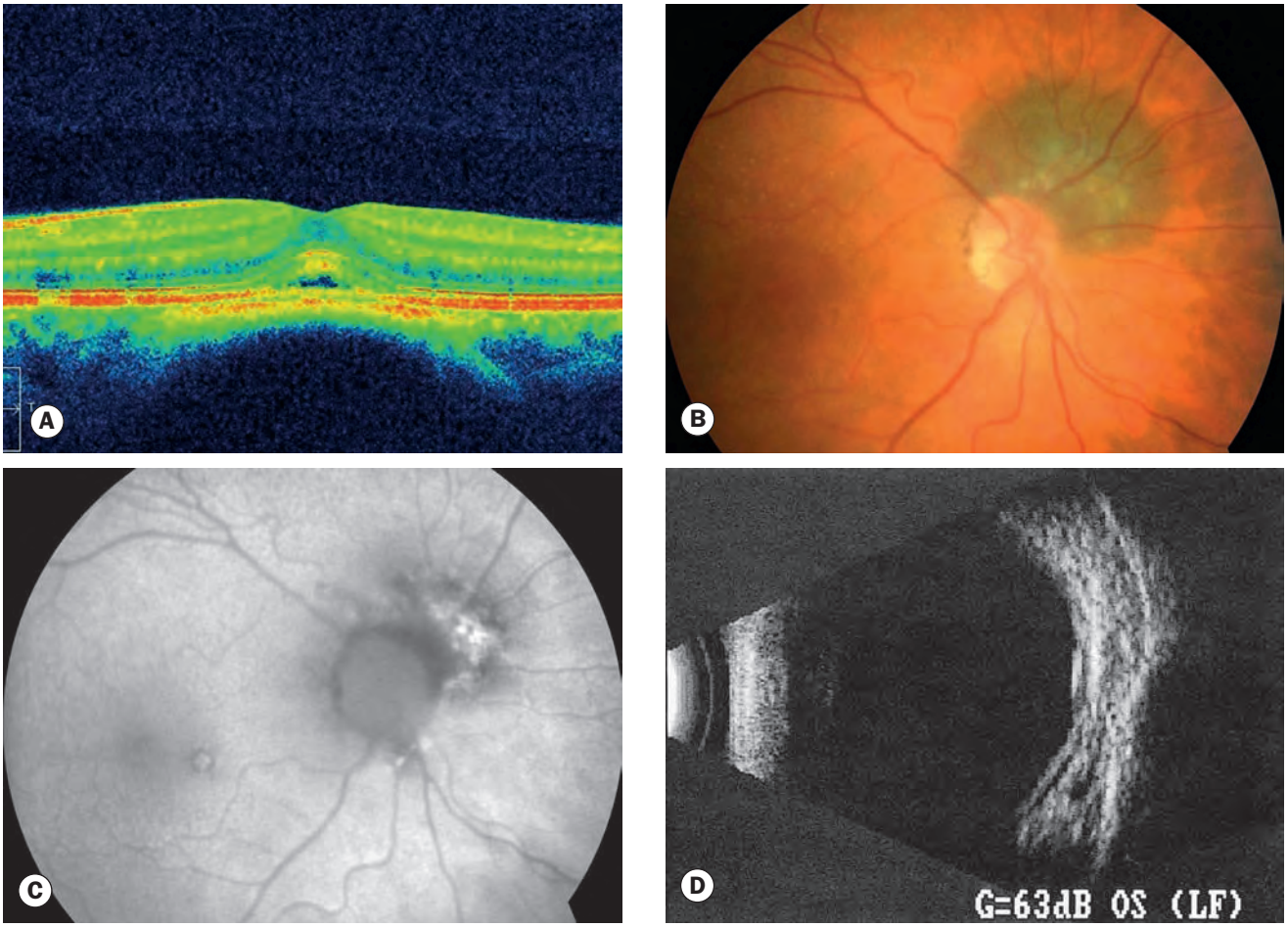


Fig 12.24 Imaging of choroidal naevi. **(A)** OCT; **(B)** and **(C)** colour photograph and fundus autofluorescence image of peripapillary naevus showing dramatic hyperautofluorescence of subtle orange pigment; **(D)** B-scan ultrasonography
(Courtesy of M Karolczak-Kulesza – fig. D)

- **Investigations**
  - Photographic documentation.
  - OCT (Fig. 12.24A) is useful for measurement of lesion thickness as well as the detection of subtle associated fluid (a high-risk factor). Secondary retinal changes tend to be more marked overlying a melanoma than a naevus.
  - Fundus autofluorescence (FAF) (Fig. 12.24B and C) can demonstrate subtle orange pigment that may not be easily discernible clinically; naevi may have patchy increased autofluorescence, but the appearance of intense diffuse or even confluent hyperautofluorescence is a useful diagnostic indicator of melanoma.
  - Fluorescein angiography (FA) is not helpful in distinguishing a melanoma from a naevus.
  - Ultrasonography (US) (Fig. 12.24D) shows a localized flat or slightly elevated lesion with high internal acoustic reflectivity; a hollow acoustic appearance is a risk factor for progression. Lesion thickness should be measured.

Treatment

- **Baseline** fundus photography and ultrasonography or OCT, with indefinite regular review.
- **Review interval** is determined by level of suspicion:
  - No suspicious features: 6 months until stability established (e.g. one year), then annual review.
  - One or two suspicious features: 4–6 months.
  - Three or more suspicious features: consider referral for ocular oncology subspecialist assessment.
- **Growth.** If growth is documented (Figs 12.25A and B) or highly suspicious features are present, the lesion should generally be regarded as a melanoma and managed accordingly.

Choroidal melanoma

Choroidal melanoma is the most common primary intraocular malignancy in adults and accounts for 80% of all uveal

Fig 12.25 Naevus growth over 5 years
(Courtesy of S Chen)

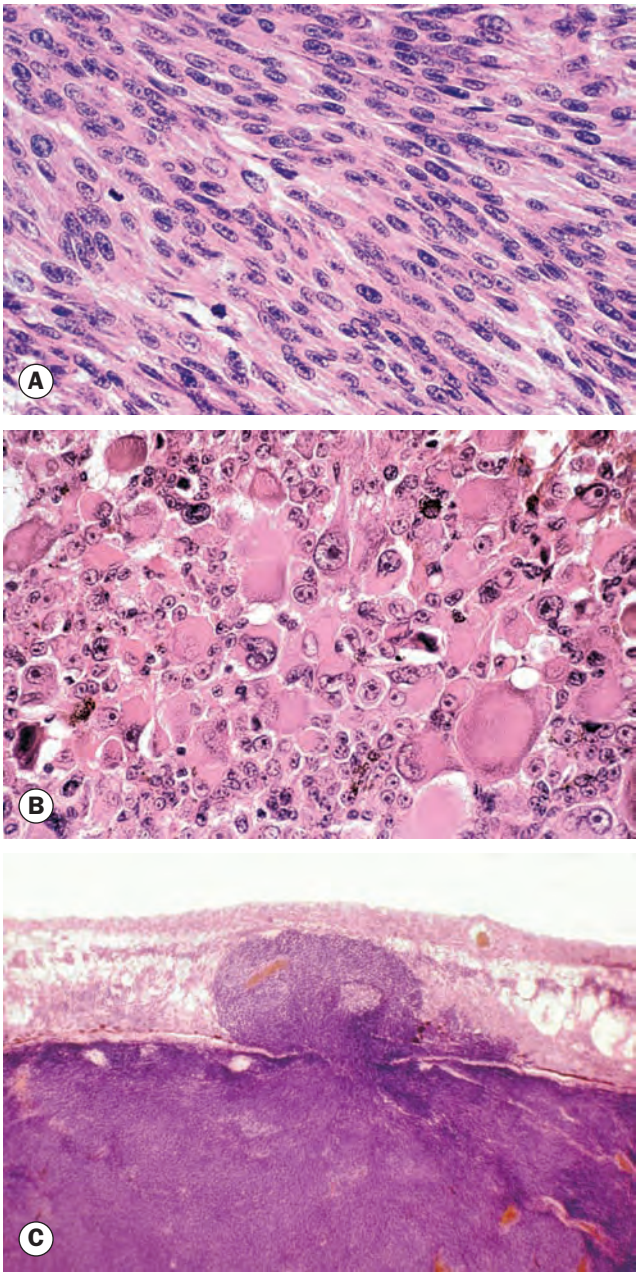


Fig. 12.26 Histology of choroidal melanoma. **(A)** Spindle cells – tightly arranged fusiform cells with indistinct cell membranes and slender or plump oval nuclei; **(B)** epithelioid cells – large pleomorphic cells with distinct cell membranes, large vesicular nuclei with prominent nucleoli, and abundant cytoplasm; **(C)** penetration of Bruch membrane in a 'collar stud' fashion
(Courtesy of J Harry – figs A and B; J Harry and G Misson, from Clinical Ophthalmic Pathology, *Butterworth-Heinemann 2001 – fig. C)*

melanomas, but is still relatively uncommon. Predisposing factors are as for iris melanoma (above). Presentation peaks at around the age of 60 years. Histopathologically, spindle (Fig. 12.26A) and epithelioid (Fig. 12.26B) cell types are seen, the former being arranged in bundles and having a better prognosis; epithelioid cells are larger and more pleomorphic with more frequent mitotic figures. Tumour composition is commonly exclusively spindle cell or a mixture of spindle and epithelioid. Lesions may penetrate Bruch membrane and the retinal pigment epithelium (RPE) with herniation into the subretinal space, classically assuming the shape of a collar stud (Fig. 12.26C). Scleral channel and vortex vein invasion can lead to orbital spread. Metastasis is commonly to the liver, bone and lung; only about 1–2% of patients have detectable metastases at the time of presentation. Mortality is up to 50% at 10 years; adverse prognostic factors include particular histological features (e.g. large numbers of epithelioid cells, mitotic activity), larger tumour dimensions, tumour genetic characteristics (e.g. somatic mutations in the tumour suppressor gene *BAP1*, present in nearly 50% of uveal melanomas, imply a greater chance of metastasis), extrascleral extension and anterior location.

Diagnosis

- **Symptoms** are often absent, with a tumour detected by chance on routine fundus examination; a range of visual disturbance can occur depending on tumour characteristics.
- **Signs**
  - A solitary elevated subretinal grey-brown (Fig. 12.27A) or rarely amelanotic (Fig. 12.27B) dome-shaped mass; diffuse infiltration is uncommon.
  - About 60% are located within 3 mm of the optic disc (Fig. 12.27C) or fovea.
  - Clumps of overlying orange pigment are common (Fig. 12.27D).
  - If the tumour breaks through the Bruch membrane it acquires a 'collar stud' (see Figs 12.26C and Fig. 12.29C) appearance.
  - Associated haemorrhage and subretinal fluid (Fig. 12.27E) are common; the latter may become bullous (Fig. 12.27F), and mask the underlying lesion.
  - Other signs can include sentinel vessels (Fig. 12.28), choroidal folds, inflammation, rubeosis iridis, secondary glaucoma and cataract.

Differential diagnosis

- **Pigmented lesions**
  - A choroidal naevus usually exhibits numerous surface drusen, without serous retinal detachment and little if any orange pigment.
  - Melanocytoma is deeply pigmented and usually located at the optic disc.
  - Congenital hypertrophy of the RPE is flat, is often grey–black and has a well-defined margin with lacunae.
  - Haemorrhage in the subretinal or suprachoroidal space, for example from choroidal neovascularization or retinal artery macroaneurysm.
  - Metastatic cutaneous melanoma has a smooth surface, a light brown colour, indistinct margins, extensive retinal detachment and often a past history of malignancy.
- **Non-pigmented lesions**
  - Circumscribed choroidal haemangioma is typically posterior, pink, dome-shaped and has a smooth surface.
  - Metastasis is often associated with exudative retinal detachment.
  - Solitary choroidal granuloma, e.g. sarcoidosis, tuberculosis.
  - Posterior scleritis, which can present with a large elevated lesion, but in contrast to melanoma pain is a common feature.
  - Large elevated choroidal neovascular lesion, which can be eccentrically located, usually in the temporal pre-equatorial region; typically associated with exudate and fresh haemorrhage, both of which rarely accompany a melanoma.
  - Prominent vortex vein ampulla is characterized by a small, smooth, brown, dome-shaped lesion, which disappears with pressure on the eye.

Investigation

Examination is sufficient for diagnosis in the majority of cases.

- **FA** is of limited diagnostic value because there is no pathognomonic pattern. The most common findings are an intrinsic tumour ('dual') circulation (Fig. 12.29A), mottled fluorescence during the arteriovenous phase and late diffuse leakage and staining. FA may, however, be useful in the differential diagnosis of simulating lesions.
- **US** is used to measure lesion dimensions and to detect tumours through opaque media and exudative retinal detachment; it may also demonstrate extraocular extension. The characteristic findings are internal homogeneity with low to medium reflectivity, choroidal excavation (Fig. 12.29B) and orbital shadowing; a basal acoustically quiet zone referred to as 'acoustic hollowing' is typical and is due to the greater tissue homogeneity in this region. A 'collar stud' configuration (Fig. 12.29C) is almost pathognomonic when present.
- **FAF.** Intense diffuse or confluent hyperautofluorescence, if present, is a useful diagnostic indicator of melanoma.
- **OCT** measures dimensions and may demonstrate associated subretinal fluid, often before clinically apparent. Secondary retinal changes are often evident overlying the lesion.
- **Indocyanine green angiography (ICGA)** usually shows hypofluorescence throughout the study and provides more information than FA about the extent of the tumour, due to lower interference from the RPE.
- **Magnetic resonance imaging (MRI)** (Fig. 12.29D) is useful to demonstrate extraocular extension and may be of some help in differential diagnosis.
- **Biopsy** is useful when the diagnosis cannot be established by less invasive methods. It may be performed either with a fine needle or using the 25-gauge vitrectomy system, the latter providing a larger sample.
- **Genetic tumour analysis** is becoming increasingly important in management, particularly with regard to prognosis; metastasis occurs almost exclusively with certain genetic profiles.
- **Systemic investigation** is directed principally towards detecting metastatic spread, though it may also be used to search for a primary tumour elsewhere if choroidal metastasis is likely. Liver function testing and ultrasonography are mainstays. Chest radiography rarely shows lung secondaries in the absence of liver disease. The comparative value of whole body PET/CT imaging is not fully defined; it has greater sensitivity for detecting metastatic disease, particularly extrahepatic lesions, but involves a substantial ionizing radiation dose.

Treatment

Treatment is performed to avoid the development of a painful and unsightly eye whilst conserving as much useful vision as possible. The extent to which ocular treatment influences survival is not yet defined, though there is some evidence that in general the risk of metastasis is lower with smaller earlier tumours. Management is individualized based on the characteristics of the particular

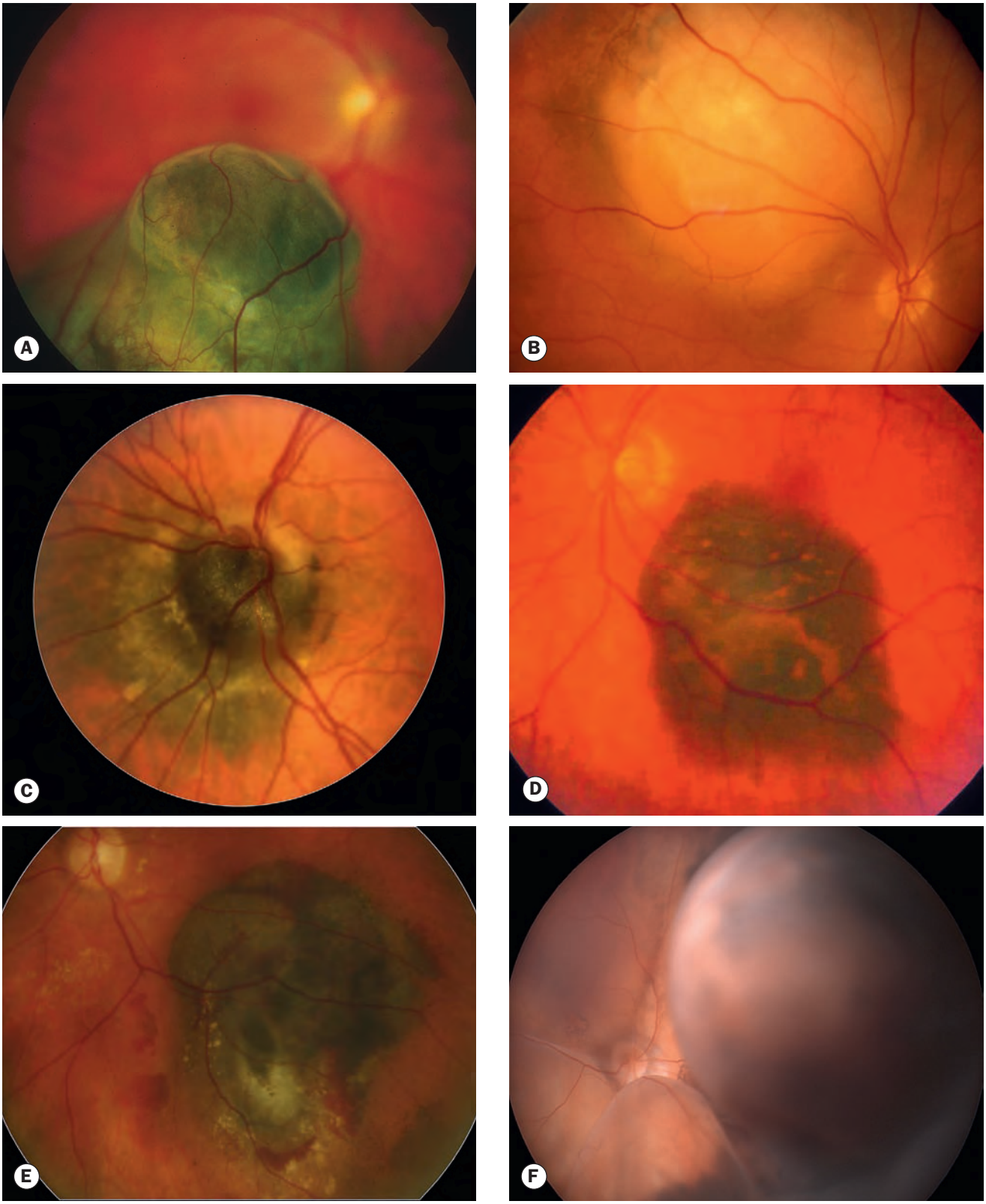


Fig. 12.27 Choroidal melanoma. **(A)** Typical pigmented melanoma; **(B)** amelanotic lesion; **(C)** melanoma of the optic disc; **(D)** overlying orange pigment; **(E)** associated haemorrhage and exudation; **(F)** extensive subretinal fluid with bullous detachment
(Courtesy of C Barry – figs A, C and E; B Damato – figs D and F)

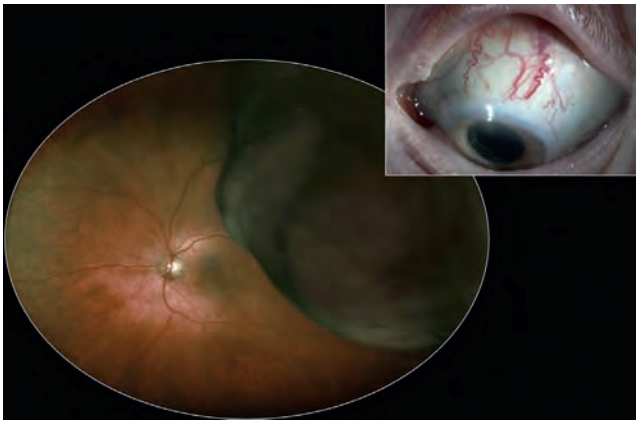


Fig. 12.28 Choroidal melanoma with overlying sentinel vessels
(Courtesy of C Barry)

tumour and the patient (e.g. general health, age, preferences, state of fellow eye).

- **Brachytherapy** (episcleral plaque radiotherapy) may be used for tumours less than 20 mm in basal diameter and up to 10 mm thick in which there is a reasonable chance of salvaging vision. Survival is similar to that following enucleation. A plaque is sutured to the sclera (Fig. 12.30A) for several days according to dosage requirement; regression begins about 1–2 months after treatment and continues over several years, leaving a flat or dome-shaped pigmented scar (Figs 12.30B and C). Complications include cataract, papillopathy (with or without disc neovascularization) and radiation retinopathy. Release of cytokines by the irradiated tumour can also cause retinopathy and other complications ('toxic tumour syndrome') that may need to be treated

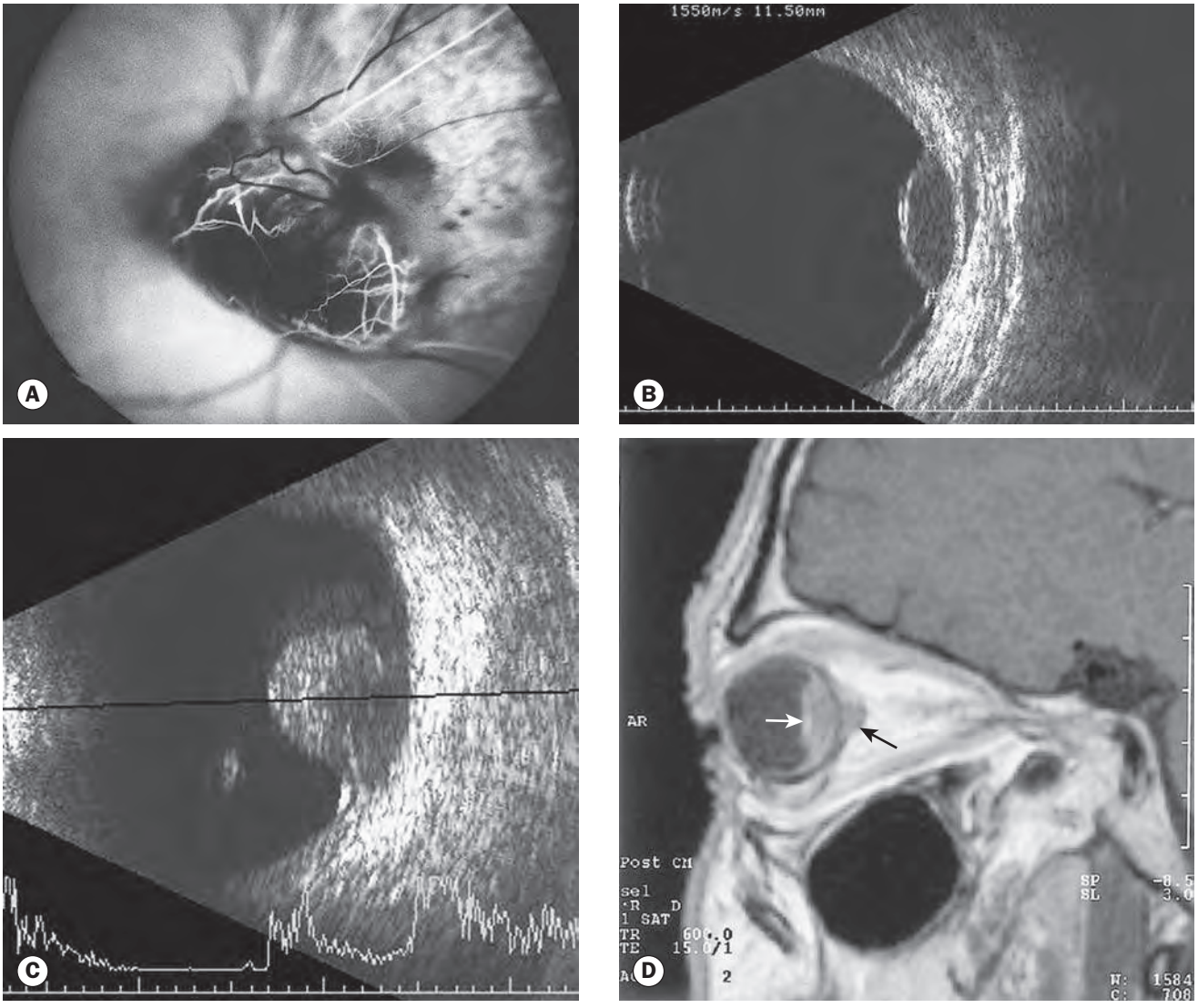


Fig. 12.29 Imaging of choroidal melanoma. **(A)** FA early phase of a 'collar stud' tumour showing a 'dual circulation'; **(B)** B-scan of a dome-shaped tumour shows choroidal excavation; **(C)** B-scan of a 'collar stud' tumour; **(D)** T1-weighted MRI shows a choroidal melanoma (white arrow) and extraocular extension (black arrow)
(Courtesy of B Damato – figs A and B; S Milewski – fig. C; M Karolczak-Kulesza – fig. D)

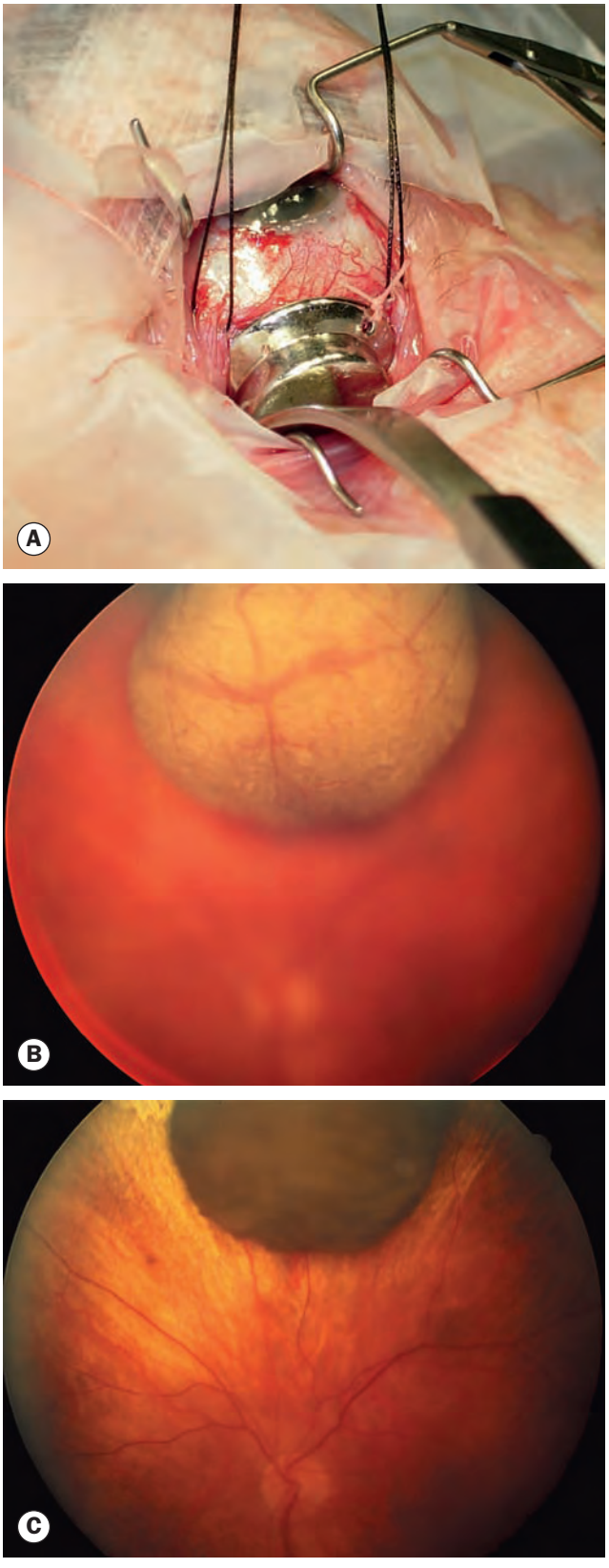


Fig. 12.30 Brachytherapy for choroidal melanoma. **(A)** Placement of plaque; **(B)** amelanotic tumour prior to treatment; **(C)** smaller pigmented lesion following treatment

(Courtesy of S Chen – fig. A; C Barry – figs B and C)

specifically (e.g. endo/exoresection, intravitreal steroid/anti-VEGF).

- **External beam radiotherapy.** Fractionated irradiation with charged particles such as protons achieves a high dose in the tumour with relative sparing of adjacent tissues, and is used for tumours unsuitable for brachytherapy either because of large size or posterior location. Targeting is aided by suturing radio-opaque tantalum markers to the sclera. Regression is slower than with brachytherapy, but survival is comparable. Intraocular complications are similar, but extraocular complications such as loss of lashes, eyelid depigmentation and keratitis may be seen.
- **Stereotactic radiotherapy** uses multiple collimated beams from different directions, either concurrently or sequentially, so that only the tumour receives a high dose of radiation. It is relatively effective, though there may be a comparatively high complication rate.
- **Transpupillary thermotherapy (TTT)** uses an infrared laser beam to induce tumour cell death by hyperthermia rather than coagulation. Indications include the treatment of a small tumour when radiotherapy is inappropriate due to poor general health. It can be used as an adjunct to radiotherapy, particularly for vision-threatening exudation. Tumour response is gradual, the lesion first becoming darker and flatter, and eventually disappearing to leave bare sclera. Complications include retinal traction, retinal tear formation with rhegmatogenous detachment, vascular occlusion and neovascularization. Local recurrence is common, especially if the tumour is thick, amelanotic or involves the disc margin.
- **Trans-scleral choroidectomy.** This is a technically difficult procedure that may be used for carefully selected tumours that are too thick for radiotherapy but less than about 16 mm in diameter. Complications include retinal detachment, hypotony, wound dehiscence and local tumour recurrence.
- **Enucleation.** Indications include large tumour size, optic disc invasion, extensive involvement of the ciliary body or angle, irreversible loss of useful vision, and poor motivation to keep the eye. It is essential to perform ophthalmoscopy after surgical draping to ensure that the correct eye is removed. Manipulation of the eye should be kept to a minimum. Orbital recurrence is rare if there is no extraocular tumour spread or if any such extension is completely excised.
- **Systemic chemotherapy** has not been shown to be of benefit in cases where there is no evidence of metastatic spread.

Circumscribed choroidal haemangioma

Circumscribed choroidal haemangioma (CCH) consists of a mass of varying-sized vascular channels within the choroid (Fig. 12.31A). It is not associated with systemic disease. It may be dormant throughout life or may give rise to symptoms, usually in early adulthood, as a result of exudative retinal detachment. Slow enlargement can occur over many years.

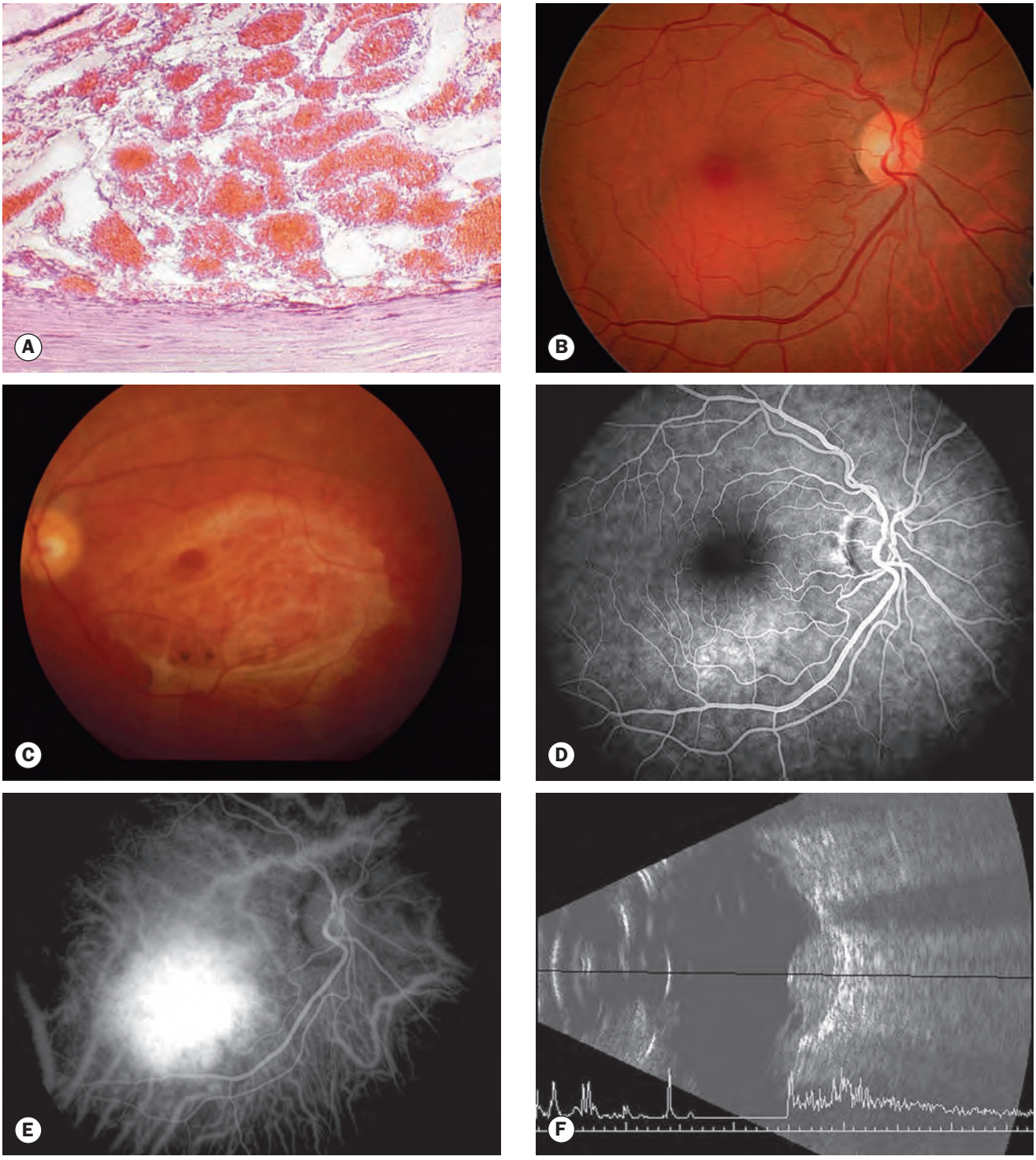


Fig. 12.31 Circumscribed choroidal haemangioma. **(A)** Histology (see text); **(B)** clinical appearance; **(C)** surface fibrous metaplasia; **(D)** FA early phase shows hyperfluorescence; **(E)** ICGA shows early hyperfluorescence; **(F)** B-scan shows an acoustically solid lesion with a sharp anterior surface and high internal reflectivity

(Courtesy of J Harry – fig. A; P Gili – figs B, D and E; B Damato – figs C and F)

Diagnosis

- **Signs**
  - An oval orange mass at the posterior pole with indistinct margins that blend with the surrounding choroid (Fig. 12.31B); median base diameter is 6 mm and median thickness 3 mm.
  - Subretinal fluid is usually present in symptomatic cases.
  - Complications include surface fibrous metaplasia (Fig. 12.31C), cystoid retinal degeneration, RPE degeneration and subretinal fibrosis.
- **OCT.** The overlying retina may be normal or show sub- and intraretinal fluid, retinoschisis and atrophy.
- **FA** reveals early spotty hyperfluorescence (Fig. 12.31D) and late diffuse but intense hyperfluorescence.
- **ICGA** provides useful diagnostic information, with strongly hyperfluorescent tumour vessels evident in the arterial phase (Fig. 12.31E), with diffuse hypofluorescence later.
- **FAF.** The lesion itself shows little or no intrinsic autofluorescence. Associated overlying orange pigment and (fresh) subretinal fluid show hyperautofluorescence, with RPE hyperplasia and atrophy giving hypoautofluorescence.
- **US** shows an acoustically solid lesion (high internal reflectivity) with a well-defined anterior surface (Fig. 12.31F).
- **MRI.** The tumour is iso- or hyperintense to the vitreous in T1-weighted images and isointense in T2-weighted images, with marked enhancement by gadolinium.

Treatment

The following may be used if vision is threatened. The superiority of any particular approach has not been established.

- **Photodynamic therapy (PDT)** using the same parameters as for choroidal neovascularization. Treatment may need to be repeated after a few months if subretinal fluid persists.
- **TTT** for lesions not involving the macula.
- **Photocoagulation** using a conventional thermal laser or micropulse treatment may be effective.
- **Radiotherapy** may be used for resistant lesions.
- **Intravitreal anti-VEGF therapy** typically reduces serous retinal detachment and can be used in combination with other modalities.
- **Oral propranolol** may be of benefit, particularly for associated exudative retinal detachment, but does not seem to consistently reduce tumour size.

Diffuse choroidal haemangioma

Diffuse choroidal haemangioma usually affects over half of the choroid and enlarges very slowly. It occurs almost exclusively in patients with Sturge–Weber syndrome ipsilateral to the naevus flammeus (see Ch. 1). The fundus has a diffuse deep red colour that is most marked at the posterior pole (Fig. 12.32A). Localized areas of thickening, simulating a circumscribed haemangioma, may be present within the larger lesion. B-scan ultrasonography shows diffuse choroidal thickening (Fig. 12.32B). Complications include secondary retinal cystoid degeneration and exudative retinal detachment; neovascular glaucoma can ensue if exudative detachment is not treated. Treatment of vision-threatening cases involves PDT or low-dose radiotherapy.

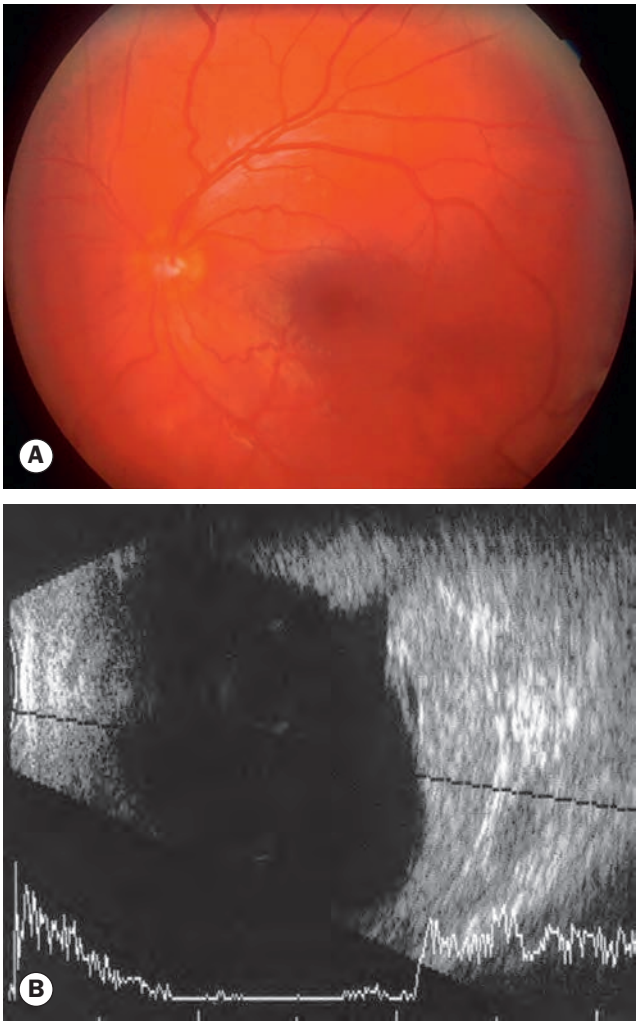


Fig. 12.32 **(A)** Diffuse choroidal haemangioma; **(B)** B-scan shows diffuse choroidal thickening
(Courtesy of B Damato – fig. B)

Optic disc melanocytoma

Melanocytoma (magnocellular naevus) is a rare, distinctive, unilateral, heavily pigmented congenital hamartoma seen most frequently in the optic nerve head but that may arise anywhere in the uvea. Histology shows large deeply pigmented polyhedral or spindle cells with small nuclei. In contrast to choroidal melanoma, melanocytomas are relatively more common in dark-skinned individuals and have a female predominance. Most cases are asymptomatic, the condition being detected on routine ophthalmoscopy (mean age 50 years). The tumour is generally stationary, and treatment is not required except in the very rare event of malignant transformation. Other complications include spontaneous tumour necrosis, optic nerve compression and retinal vein obstruction.

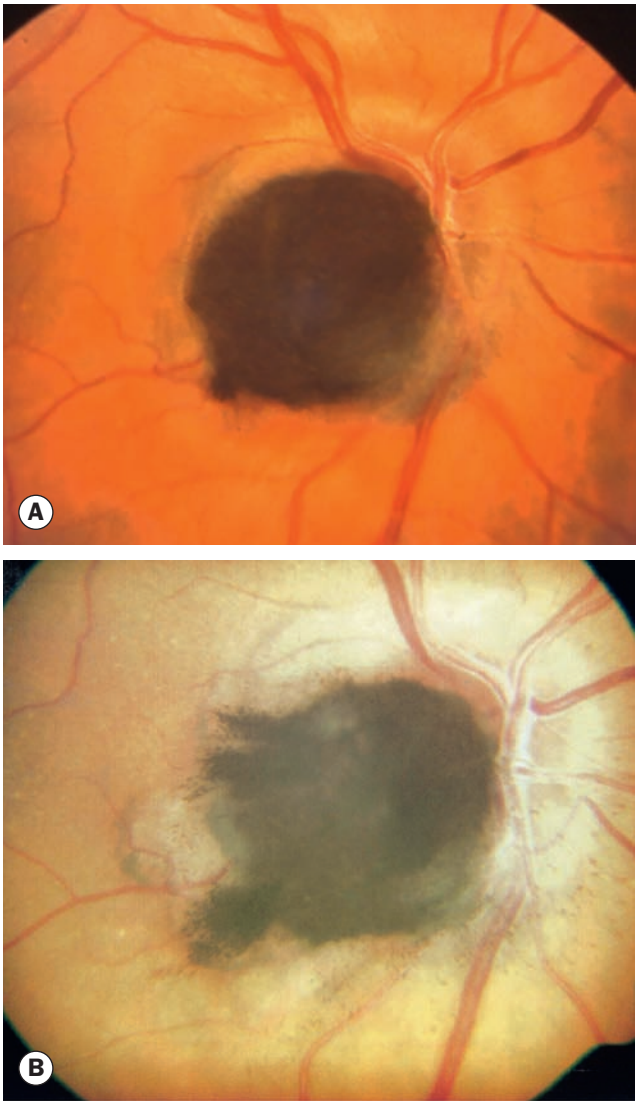


Fig. 12.33 Melanocytoma. **(A)** and **(B)** The same lesion at baseline and 11 years later
(Courtesy of S Chen)

Diagnosis

- A dark brown or black, flat or slightly elevated lesion with feathery edges that may extend over the edge of the disc (Figs 12.33A and B).
- Occasionally a large tumour occupies most of the disc surface and may lead to pigment dispersion into the vitreous.
- A relative afferent pupillary defect may be present, even if visual acuity (VA) is good.
- FA shows persistent dense hypofluorescence due to masking.

Choroidal osteoma

Choroidal osteoma is a rare benign ossifying tumour that has a strong female preponderance; patients are often young adults. Both eyes are affected in about 10–20%. Histology shows mature cancellous bone, with overlying RPE atrophy. Presentation is in the second–third decades. Masquerading lesions include osseous metaplasia in association with a choroidal haemangioma, and sclerochoroidal calcification, the latter characterized by multiple geographical yellow–white fundus lesions that usually involve both eyes of an older adult.

Diagnosis

- **Symptoms.** Gradual visual impairment if the macula is involved by the tumour itself, or occasionally more rapid deterioration secondary to choroidal neovascularization.
- **Signs**
  - Initially orange, maturing lesions appear yellow–white; they are flat or minimally elevated with well-defined, scalloped margins near the disc or at the posterior pole (Figs 12.34A–D).
  - Spider-like fine vessels and bone-spicule RPE changes may develop (Fig. 12.34B).
  - Slow growth may occur over several years (Figs 12.34C and D).
  - Spontaneous resorption and decalcification may rarely occur.
  - The visual prognosis is poor if the lesion involves the fovea.
- **OCT** demonstrates overlying retinal changes, with enhanced depth imaging showing a lattice pattern in calcified tumour similar to the appearance of cancellous bone.
- **FA** manifests early, irregular, diffuse mottled hyperfluorescence and late staining (Fig. 12.35A).
- **FAF** shows mainly isoautofluorescence in calcified areas and hypoautofluorescence in decalcified regions.
- **ICGA** shows early hypofluorescence (Fig. 12.35B) and late staining. The tumour appears larger than on clinical examination.
- **US** shows a highly reflective anterior surface and orbital shadowing (Fig. 12.35C).
- **CT** demonstrates a dense plaque-like opacity at the level of the choroid (Fig. 12.35D).

Metastatic tumours

The choroid is by far the most common (90%) site for uveal metastases. The most frequent primary sites are the breast and bronchus. A choroidal secondary may be the initial presentation of a bronchial carcinoma, whereas a past history of breast cancer is the rule in patients with breast secondaries. Other less common primary sites include the gastrointestinal tract, kidney and skin (melanoma). The prostate is an extremely rare primary site. Survival is generally poor, with a median of 8–12 months.

Diagnosis

- **Symptoms.** Visual impairment may occur due to macular involvement by the lesion itself or associated exudative retinal detachment. A minority are discovered incidentally.

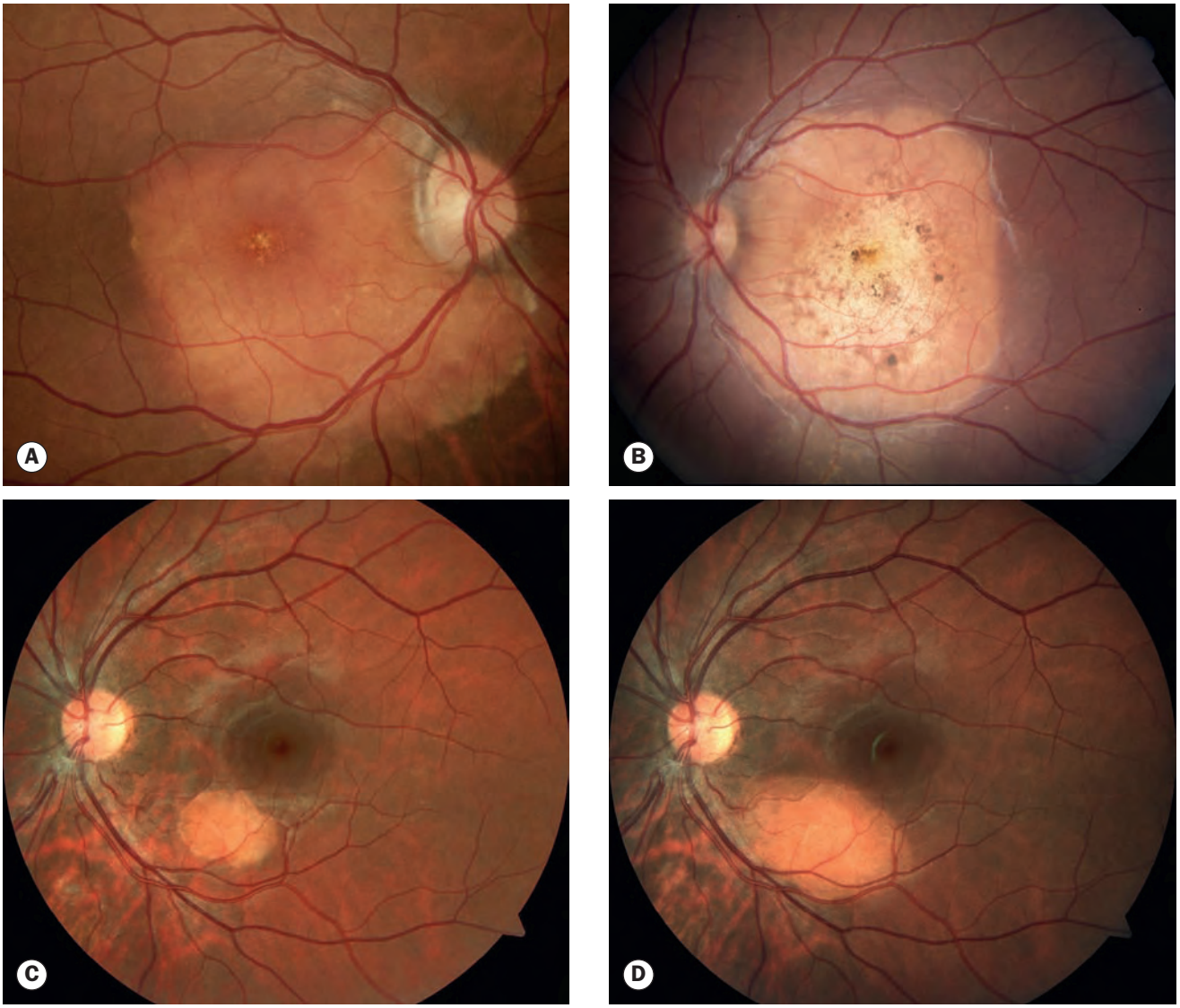


Fig. 12.34 Choroidal osteoma. **(A)** Large macular lesion; **(B)** overlying RPE changes; **(C)** and **(D)** growth over 5 years
(Courtesy of S Chen)

- **Signs**
  - The most common appearance is a fast-growing yellowish slightly elevated placoid lesion with indistinct margins, typically at the posterior pole and often multifocal and bilateral (10–30% – Figs 12.36A and B); overlying pigmentary changes are fairly common (Fig. 12.36C).
  - Melanoma secondaries are usually pigmented.
  - Secondary exudative retinal detachment is frequent and may occur in eyes with relatively small lesions.
- **US** may be useful in detection, particularly to demonstrate a lesion underlying exudative retinal detachment. A placoid tumour shows diffuse choroidal thickening; a larger dome-shaped lesion shows moderately high internal acoustic reflectivity (Fig. 12.36D).
- **OCT** shows overlying RPE thickening and photoreceptor irregularity, with subretinal fluid when present. Enhanced depth imaging OCT shows choriocapillaris thinning overlying the tumour.
- **FA** shows early hypofluorescence and diffuse late staining, but in contrast to choroidal melanoma a dual circulation is not seen.
- **ICGA** usually shows hypofluorescence through the study and may show additional deposits not evident on clinical examination or FA.
- **Biopsy** by fine needle aspiration or using a 25-gauge vitrectomy system may be appropriate when the primary site is unknown.
- **Systemic investigation** is directed at locating the primary tumour, if unknown, and other metastatic sites. The list below is not exhaustive.
  - Full history and physical examination.
  - Mammography.
  - Chest radiography and sputum cytology.

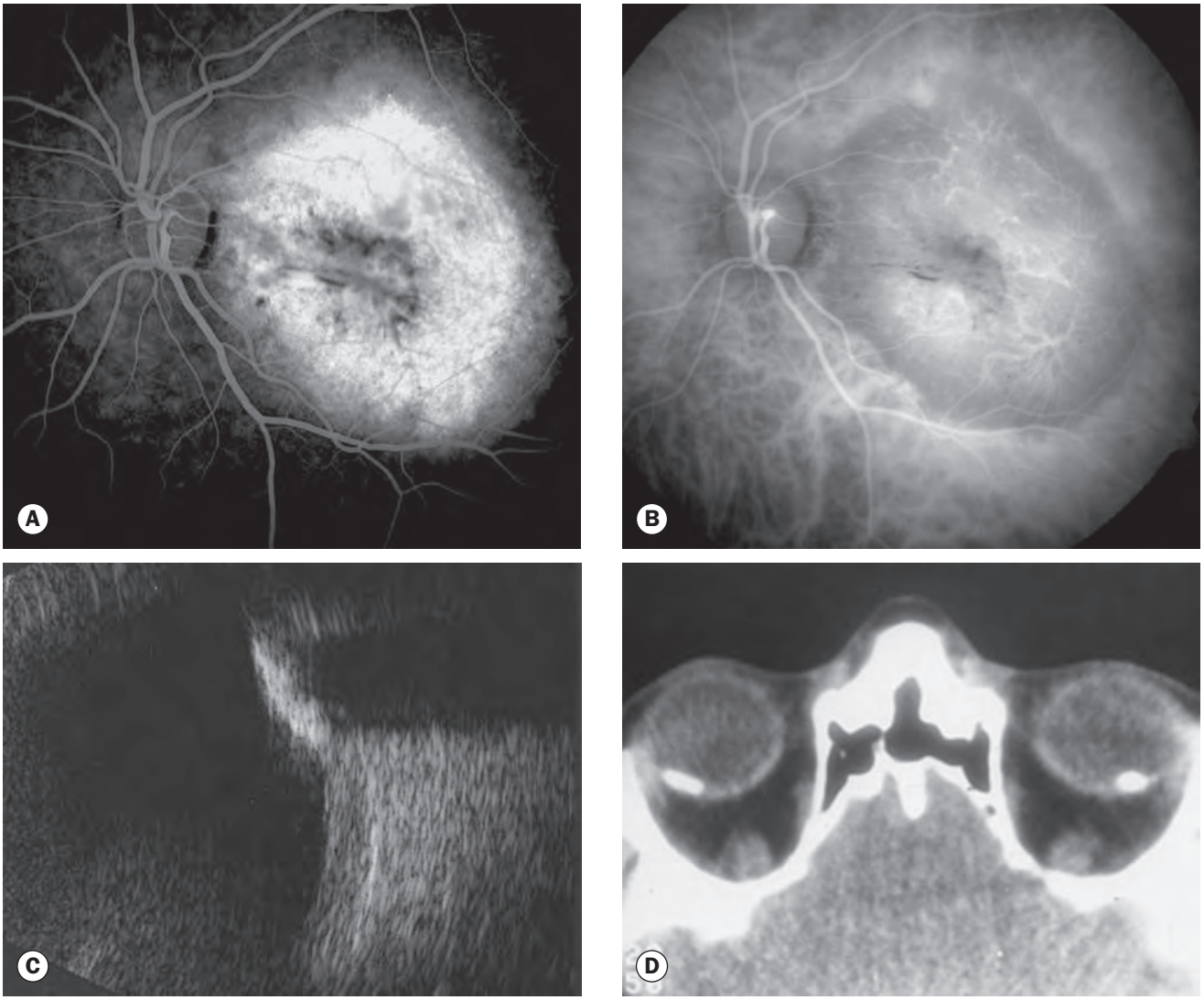


Fig. 12.35 Imaging of choroidal osteoma. **(A)** FA late phase shows mottled hyperfluorescence; **(B)** ICGA early phase shows hypofluorescence; **(C)** B-scan shows a highly reflective anterior surface and orbital shadowing; **(D)** axial CT demonstrates bilateral lesions with similar consistency to bone
(Courtesy P Gili – figs A and B)

- Liver function tests.
- Abdominal or whole body scans.
- Faecal occult blood.
- Urinalysis for red blood cells.
- Abdominal ultrasound.
- Whole-body imaging, e.g. PET/CT, MRI.

Treatment

- **Observation**, if the patient is asymptomatic or receiving systemic chemotherapy, which may also be beneficial for choroidal metastases.
- **Radiotherapy**, either external beam or brachytherapy, typically for solitary lesions.
- **TTT** is useful for small tumours with minimal subretinal fluid.
- **Anti-VEGF treatment** may lead to regression of metastases in some cases, as well as addressing secondary phenomena such as subretinal fluid accumulation. It is probably more effective in small early lesions.

NEURAL RETINAL TUMOURS

Retinoblastoma

Introduction

Retinoblastoma is rare, occurring in up to 1:18 000 live births, but is the most common primary intraocular malignancy of childhood and accounts for about 3% of all childhood cancers. After uveal

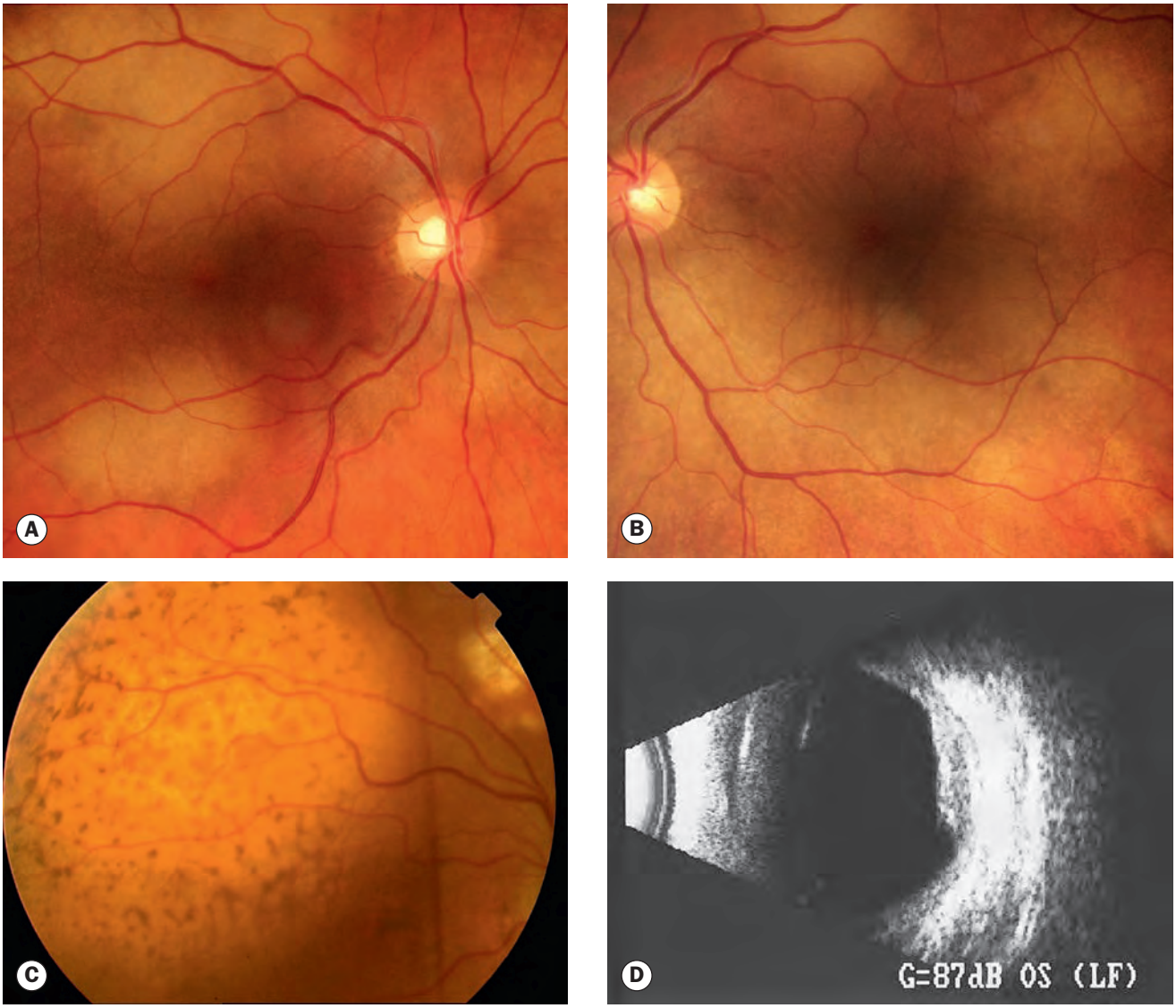


Fig. 12.36 Choroidal metastasis. **(A)** and **(B)** Bilateral multifocal metastases from a breast primary – regression in response to systemic chemotherapy is beginning in the left eye; **(C)** overlying pigmentary stippling; **(D)** B-scan showing moderate internal reflectivity

(Courtesy of C Barry – figs A and B; B Damato – fig. C)

melanoma, it is the second most common malignant intraocular tumour. Survival rates are over 95% in specialized centres, with preservation of vision in a majority of eyes, but are much lower in the developing world. Tumours are composed of small basophilic cells (retinoblasts) with large hyperchromatic nuclei and scanty cytoplasm. Many retinoblastomas are undifferentiated but varying degrees of differentiation are characterized by the formation of structures known as rosettes (Flexner–Wintersteiner, Homer–Wright and fleurettes – Fig. 12.37A). Growth (Fig. 12.37B) may be endophytic (into the vitreous) with seeding of tumour cells throughout the eye, or exophytic (into the subretinal space) leading to retinal detachment, or mixed, or the retina may be diffusely infiltrated. Optic nerve invasion (Fig. 12.37C) may occur, with spread of tumour along the subarachnoid space to the brain. Metastatic spread is to regional nodes, lung, brain and bone.

Genetics

The genetics of retinoblastoma are often highlighted as a paradigm illustrating the genetic basis of cancer. The tumour suppressor gene in which mutations predisposing to retinoblastoma occur is *RB1*; over 900 different mutations have been reported to date. The size of a gene deletion tends to correlate with aggressive retinoblastoma behaviour. Mutations in *RB1* or associated genes in a common pathway are also disrupted in many sporadic tumours. Modifier genes for retinoblastoma have also been identified and may constitute therapeutic targets.

- **Heritable** (hereditary, germline) retinoblastoma accounts for 40%. In heritable retinoblastoma one of the pair of alleles of *RB1* is mutated in all the cells in the body. When a further mutagenic event ('second hit' according to the 'two-hit'

Fig. 12.37 Pathology of retinoblastoma. **(A)** well-differentiated tumour showing abundant Flexner–Wintersteiner rosettes; **(B)** whole eye section showing both endophytic and exophytic growth; **(C)** transverse section of the cut end of an optic nerve demonstrating an area of tumour infiltration *(Courtesy of J Harry)*

hypothesis proposed by Knudson) affects the second allele, the cell may then undergo malignant transformation. Because of the presence of the mutation in all cells, a large majority of these children develop bilateral and multifocal tumours. Heritable retinoblastoma patients also have a predisposition to non-ocular cancers such as pinealoblastoma ('trilateral retinoblastoma', which occurs in up to 10%, usually before the age of 5), osteosarcomas, soft tissue sarcomas and melanomas; each of these tends to occur in a particular age group. The risk of a second malignancy is about 6% but this increases five-fold if external beam irradiation has been used to treat the original tumour, the second tumour tending to arise within the irradiated field.

- **Non-heritable** (non-hereditary, somatic) retinoblastoma. The tumour is unilateral, not transmissible and does not predispose the patient to second non-ocular cancers. If a patient has a solitary retinoblastoma and no positive family history, this is almost certainly (but not conclusively) non-heritable so that the risk in each sibling and the patient's offspring is about 1%. Ninety per cent of children with unilateral retinoblastoma will have the non-hereditary form.
- **Screening of at-risk family members.** Germline mutations are autosomal dominant and so transmitted to 50%, but because of incomplete penetrance only 40% of offspring will be affected. Detection of mutations in *RB1* has approached 95% in recent years. Once identified in a particular child, the same mutation can be sought in siblings, its presence confirming their high-risk status. Siblings at risk of retinoblastoma should be screened by prenatal ultrasonography, by ophthalmoscopy soon after birth and then regularly until the age of 4 or 5 years. Early diagnosis correlates with a higher chance of preserving vision, salvaging the eye and preserving life. If a child has heritable retinoblastoma, the risk to siblings is 2% if the parents are healthy, and 40% if a parent is affected. It is important that all family members, including the parents, are examined for the presence of retinoblastoma-associated eye lesions (retinomas, calcified retinal scars, phthisis).

Clinical features

- **Presentation** is within the first year of life in bilateral cases and around 2 years of age if the tumour is unilateral. Careful enquiry about a family history of ocular tumours is critical.
  - Leukocoria (white pupillary reflex) is the commonest presentation (60%) and may first be noticed in family photographs (Fig. 12.38A).
  - Strabismus is the second most common (20%); fundus examination is therefore mandatory in all cases of childhood squint.
  - Painful red eye with secondary glaucoma, which may occasionally be associated with buphthalmos (Fig. 12.38B).
  - Poor vision.
  - Inflammation or pseudoinflammation (Figs 12.38C and D).

Fig. 12.38 Presentation of retinoblastoma. **(A)** Leukocoria; **(B)** secondary glaucoma and buphthalmos; **(C)** red eye due to uveitis; **(D)** iris nodules and pseudohypopyon; **(E)** orbital inflammation; **(F)** orbital invasion
(Courtesy of C Barry – fig. A; N Rogers – fig. B; U Raina – fig. C)

- Routine examination of a patient known to be at risk.
- Orbital inflammation mimicking orbital or preseptal cellulitis may occur with necrotic tumours (Fig. 12.38E).
- Orbital invasion or visible extraocular growth may occur in neglected cases (Fig. 12.38F).
- Metastatic disease involving regional lymph nodes and brain before the detection of ocular involvement is rare.

- **Signs**
  - An intraretinal tumour is a homogeneous, dome-shaped white lesion (Fig. 12.39A) that becomes irregular, often with white flecks of calcification.
  - An endophytic tumour projects into the vitreous as a white mass that may 'seed' into the gel (Figs 12.39B).
  - An exophytic tumour forms multilobular subretinal white masses and causes overlying retinal detachment (Figs 12.39C and D).

Investigation

- **Red reflex testing** with a direct ophthalmoscope is a simple screening test for leukocoria that is easily employed in the community.
- **Examination under anaesthesia** includes the following:
  - General examination for congenital abnormalities of the face and hands.
  - Tonometry.
  - Measurement of the corneal diameter.

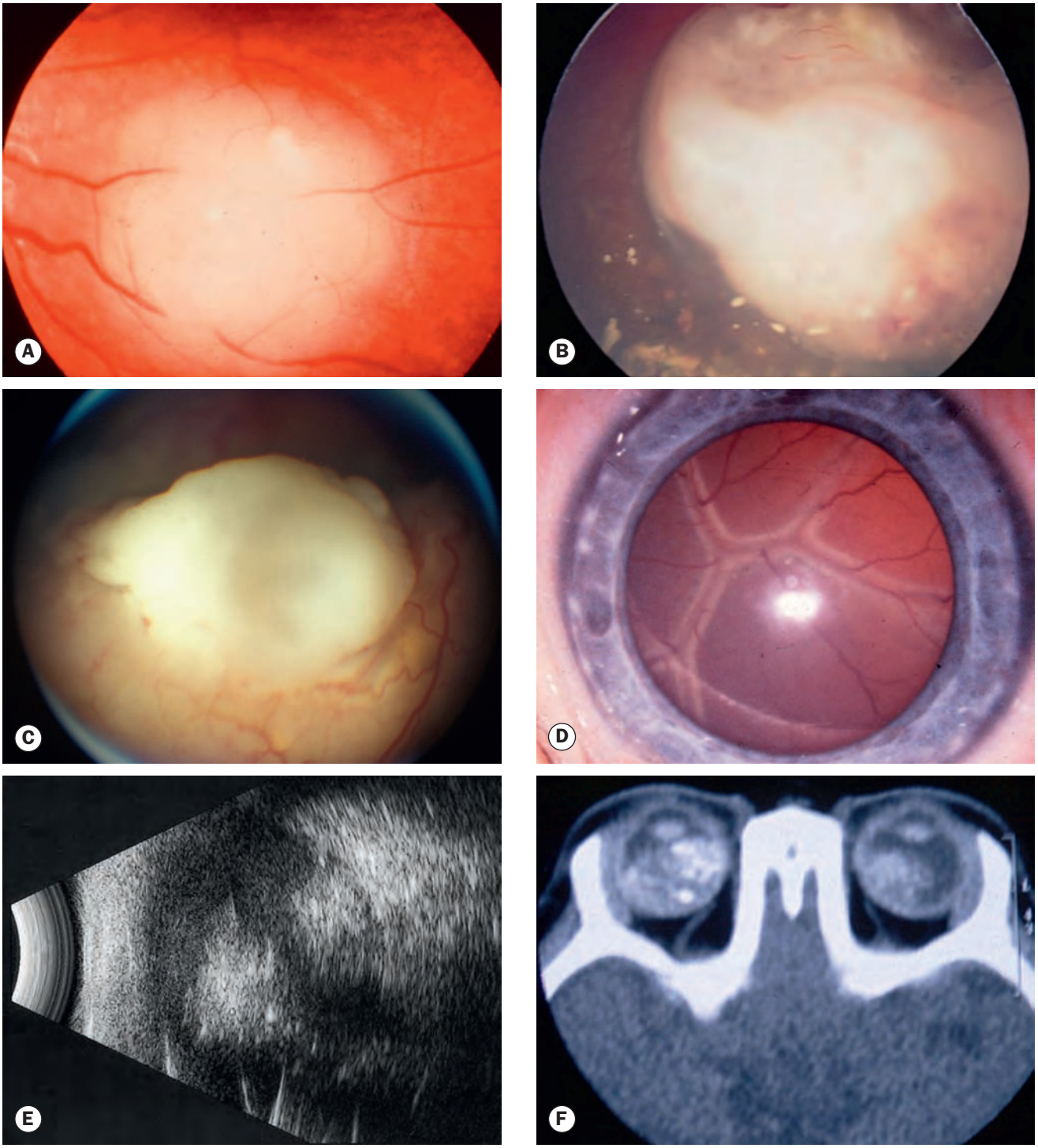


Fig. 12.39 Retinoblastoma. **(A)** Intraretinal tumour; **(B)** endophytic tumour with vitreous seeding; **(C)** mixed endophytic and exophytic growth; **(D)** total retinal detachment; **(E)** B-scan shows echoes from calcification; **(F)** axial CT shows bilateral tumours with calcification

(Courtesy of B Dixon-Romanowska – fig. B; L MacKeen – fig. C; K Nischal – fig. F)

- Anterior chamber examination with a hand-held slit lamp.
- Ophthalmoscopy, documenting all findings with colour drawings or photography.
- Cycloplegic refraction.

- **US** is used mainly to assess tumour size. It also detects calcification (Fig. 12.39E) within the tumour and is helpful in the exclusion of simulating lesions such as Coats disease.
- **Wide-field photography** (portable if necessary) is useful for both surveying and documentation, and offers particular advantages in the management of retinoblastoma.
- **CT** also detects calcification (Fig. 12.39F) but entails a significant dose of radiation so is avoided by many practitioners. Plain X-rays may be used to detect calcification in resource-poor regions.
- **MRI** does not detect calcification but is useful for optic nerve evaluation, detection of extraocular extension and pinealoblastoma, and to aid differentiation from simulating conditions.
- **Systemic assessment** includes physical examination and MRI scans of the orbit and skull as a minimum in high-risk cases. If these indicate the presence of metastatic disease then bone scans, bone marrow aspiration and lumbar puncture are also performed.
- **Genetic studies** on tumour tissue and blood samples from the patient and relatives.

Treatment

The approach to management is collaborative between the ophthalmologist, paediatric oncologist, ocular pathologist, geneticist, allied health professionals and parents. Treatment is highly individualized.

- **Chemotherapy** is a mainstay of treatment in most cases, and may be used in conjunction with local treatments (focal consolidation – see below). Intravenous carboplatin, etoposide and vincristine (CEV) are given in three to six cycles according to the grade of retinoblastoma. Single- (carboplatin alone) or dual-agent therapy has also given favourable results in some circumstances, such as bridging therapy to allow deferral of more aggressive measures. Selective ophthalmic artery infusion has shown promising outcomes and study is ongoing. Intravitreal melphalan seems to be effective for vitreous seeding, though carries a very small risk of extraocular dissemination. Sub-Tenon carboplatin injection is now less commonly used given the availability of effective alternatives. Chemoreduction may be followed by focal treatment with cryotherapy or TTT to consolidate tumour control.
- **TTT** achieves focal consolidation following chemotherapy, or is sometimes used as an isolated treatment. Focal techniques such as TTT and cryotherapy exert both a direct effect and probably increase susceptibility to the effects of chemotherapy.

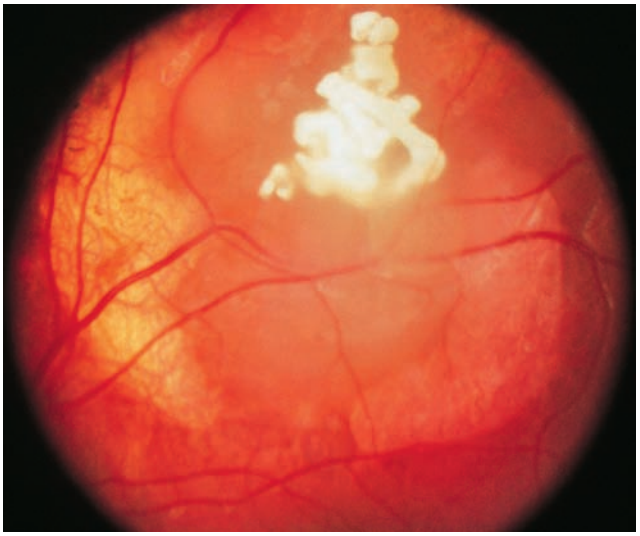


Fig. 12.40 Retinoblastoma – regression after brachytherapy

- **Cryotherapy** using a triple freeze–thaw technique is useful for pre-equatorial tumours without either deep invasion or vitreous seeding.
- **Brachytherapy** using a radioactive plaque can be utilized for an anterior tumour if there is no vitreous seeding, and in other circumstances such as resistance to chemotherapy (Fig. 12.40).
- **External beam radiotherapy** is avoided if possible, particularly in patients with heritable retinoblastoma because of the risk of inducing a second malignancy; retinoblastoma is highly radiation-sensitive, however. Adverse effects include cataract, radiation neuropathy, radiation retinopathy and hypoplasia of the bony orbit.
- **Enucleation** is generally indicated if there is neovascular glaucoma, anterior chamber infiltration, optic nerve invasion or if a tumour occupies more than half the vitreous volume. It is also considered if chemoreduction fails and is useful for diffuse retinoblastoma because of a poor visual prognosis and a high risk of recurrence with other modalities. Enucleation should be performed with minimal manipulation and it is imperative to excise a section of optic nerve to at least 10 mm.
- **Extraocular extension**
  - Adjuvant chemotherapy consisting of a 6-month course of CEV is given subsequent to enucleation at some centres if there is retrolaminar or massive choroidal spread.
  - External beam radiotherapy is indicated when there is tumour extension to the cut end of the optic nerve at enucleation, or extension through the sclera.
- **Review.** Careful review at frequent intervals is generally required following treatment, in order to detect recurrence or the development of a new tumour, particularly in heritable disease.

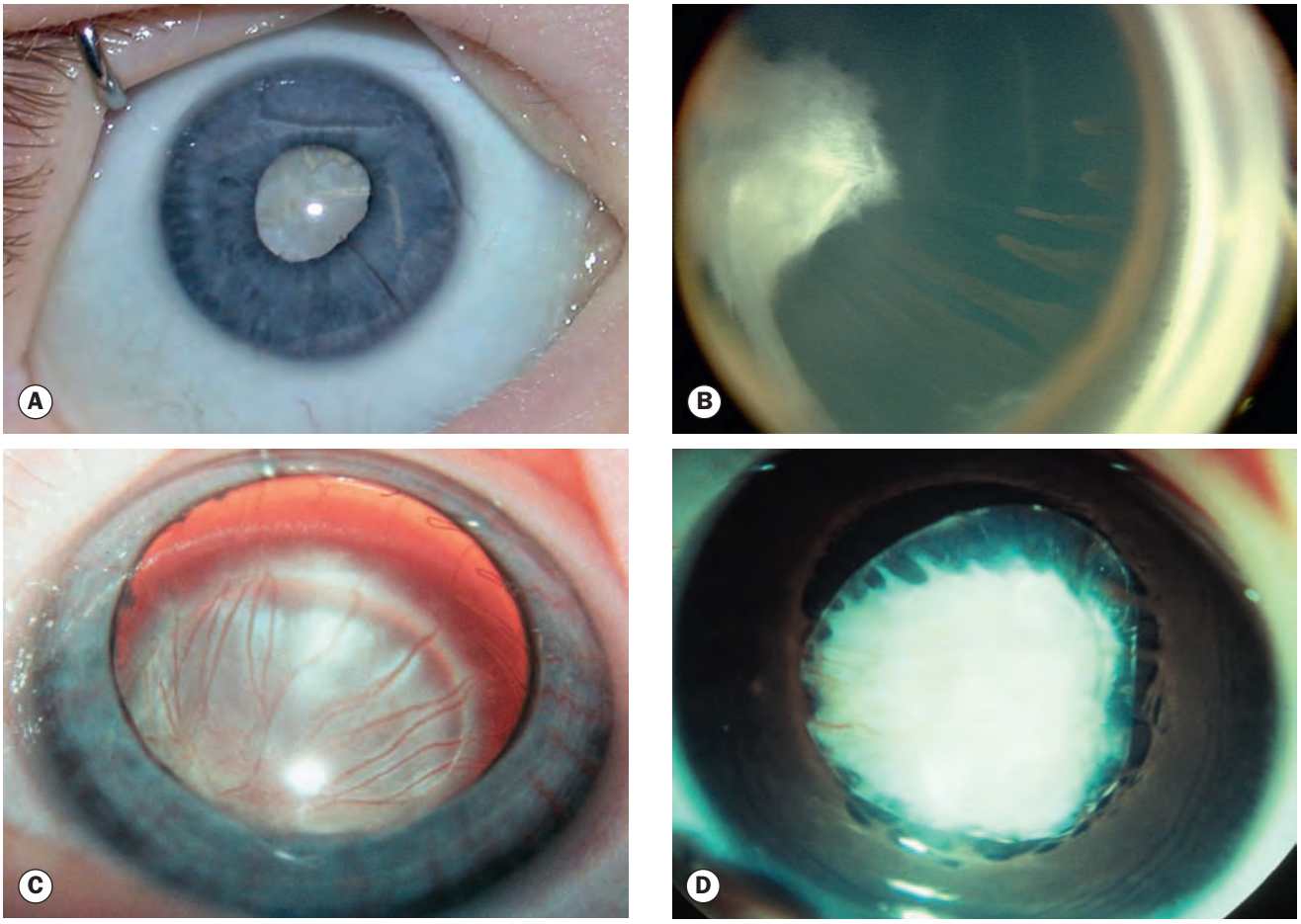


Fig. 12.41 Persistent anterior fetal vasculature. **(A)** Leukocoria with secondary cataract; **(B)** retrolental mass with elongated ciliary processes; **(C)** retrolental vessels and less dense fibrosis; **(D)** dense plaque with secondary lens changes
(Courtesy of S Chen – fig. A; Hospital for Sick Children, Toronto – fig. B; K Nischal – figs C and D)

Differential diagnosis

- **Persistent anterior fetal vasculature** (persistent hyperplastic primary vitreous – see also Ch. 17) is confined to the anterior segment and often involves the lens.
  - Presentation is with leukocoria (Fig. 12.41A) involving a retrolental mass into which elongated ciliary processes are inserted (Fig. 12.41B).
  - The size and density of the retrolental fibrovascular tissue is variable (Fig. 12.41C).
  - Complications include cataract (Fig. 12.41D) and angle-closure glaucoma.
  - Early lens and vitreoretinal surgery may preserve useful vision in some cases.
- **Persistent posterior fetal vasculature** is confined to the posterior segment and the lens is usually clear.
  - Presentation is with leukocoria, strabismus or nystagmus.
  - A dense fold of condensed vitreous and retina extends from the optic disc to the ora serrata (Fig. 12.42).
  - Treatment is not effective.
- **Coats disease** is almost always unilateral, more common in boys and tends to present later than retinoblastoma (see Ch. 13).

Fig. 12.42 Persistent posterior fetal vasculature

- **Retinopathy of prematurity**, if advanced, may cause retinal detachment and leukocoria. Diagnosis is usually straightforward because of the history of prematurity and low birth weight (see Ch. 13).
- **Toxocariasis**. Chronic *Toxocara* endophthalmitis (see Ch. 11) may cause a cyclitic membrane and a white pupil. A granuloma at the posterior pole may resemble an endophytic retinoblastoma.
- **Uveitis** may mimic the diffuse infiltrating type of retinoblastoma seen in older children. Conversely, retinoblastoma may be mistaken for uveitis, endophthalmitis or orbital cellulitis.
- **Vitreoretinal dysplasia** is caused by faulty differentiation of the retina and vitreous that results in a detached dysplastic retina forming a retrolental mass with leukocoria (Fig. 12.43). Other features include microphthalmos, shallow anterior chamber and elongated ciliary processes. Dysplasia may occur in isolation or in association with systemic abnormalities:
  - Norrie disease is an X-linked recessive disorder in which affected males are blind at birth or early infancy. It is caused by mutations in the *NDP* gene. Systemic features include cochlear deafness and mental retardation.
  - Incontinentia pigmenti is an X-linked dominant condition that is lethal *in utero* for boys. Mutations have been found in the *NEMO* gene. It is characterized by a vesiculobullous rash on the trunk and extremities that with time is replaced by linear pigmentation. Other features include malformation of teeth, hair, nails, bones and CNS.
  - Walker–Warburg syndrome is an autosomal recessive condition characterized by absence of cortical gyri and cerebellar malformations that may be associated with hydrocephalus and encephalocele. Neonatal death is common and survivors suffer severe developmental delay. Apart from vitreoretinal dysplasia other ocular features include Peters anomaly, cataract, uveal coloboma, microphthalmos and optic nerve hypoplasia.
- **Other tumours**
  - Retinoma (retinocytoma) is a variant of retinoblastoma that generally exhibits benign behaviour but has a genetic profile indicating premalignancy – rarely, a retinoma can undergo late transformation into a rapidly growing retinoblastoma. It manifests as a smooth whitish dome-shaped lesion, which typically involutes spontaneously to a calcified mass associated with RPE alteration and chorioretinal atrophy (Fig. 12.44).
  - Retinal astrocytoma, which may be multifocal and bilateral (see below).

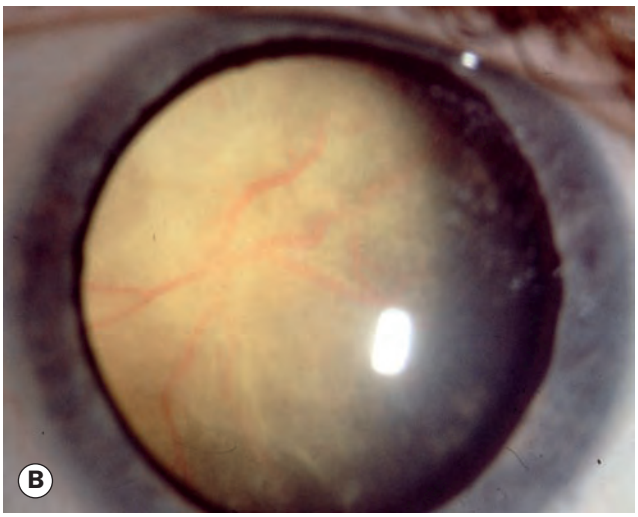


Fig. 12.43 Vitreoretinal dysplasia. **(A)** Pathological specimen; **(B)** clinical appearance

(Courtesy of J Harry and G Misson, from Clinical Ophthalmic Pathology, *Butterworth-Heinemann 2001 – fig. A)*

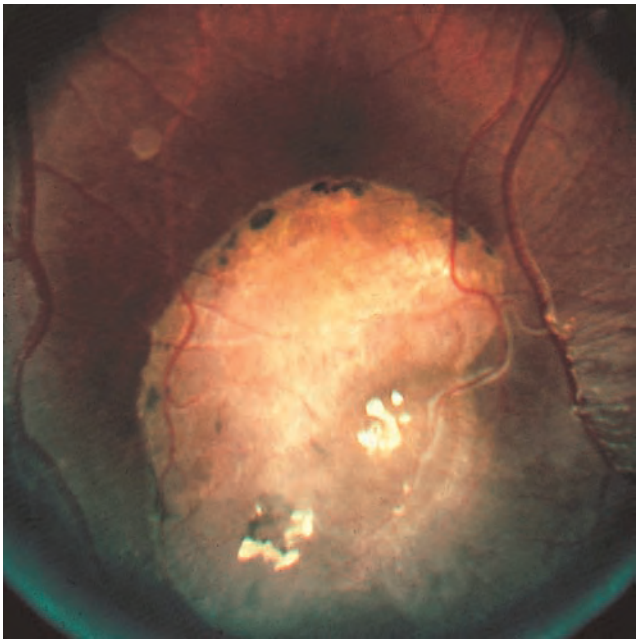


Fig. 12.44 Retinoma

Retinal astrocytoma

Introduction

Astrocytoma (astrocytic hamartoma) of the retina and optic nerve head is rare; it frequently does not threaten vision or require treatment. Most are endophytic, protruding into the vitreous, but exophytic subretinal tumours can occur. Astrocytomas may be encountered as incidental solitary lesions in normal individuals but are most frequently seen in tuberous sclerosis (see below) and occasionally in association with neurofibromatosis type 1 and retinitis pigmentosa. About 50% of patients with tuberous sclerosis have one or more astrocytomas, which may be bilateral.

Diagnosis

- **Symptoms.** Most tumours are asymptomatic and detected on screening for tuberous sclerosis; isolated lesions unassociated with known systemic disease are usually found at a routine eye examination.
- **Signs.** A yellowish or white semitransparent plaque, nodule or mulberry-like lesion, often semitransparent in its periphery and calcified centrally (Fig. 12.45A).
- **Lesions can be large** (Fig. 12.45B) and/or have a cystic component (Fig. 12.45C); growth with vision-threatening complications can occur.
- **OCT** shows a granular hyper-reflective appearance of the retinal layers with relative sparing of underlying RPE.

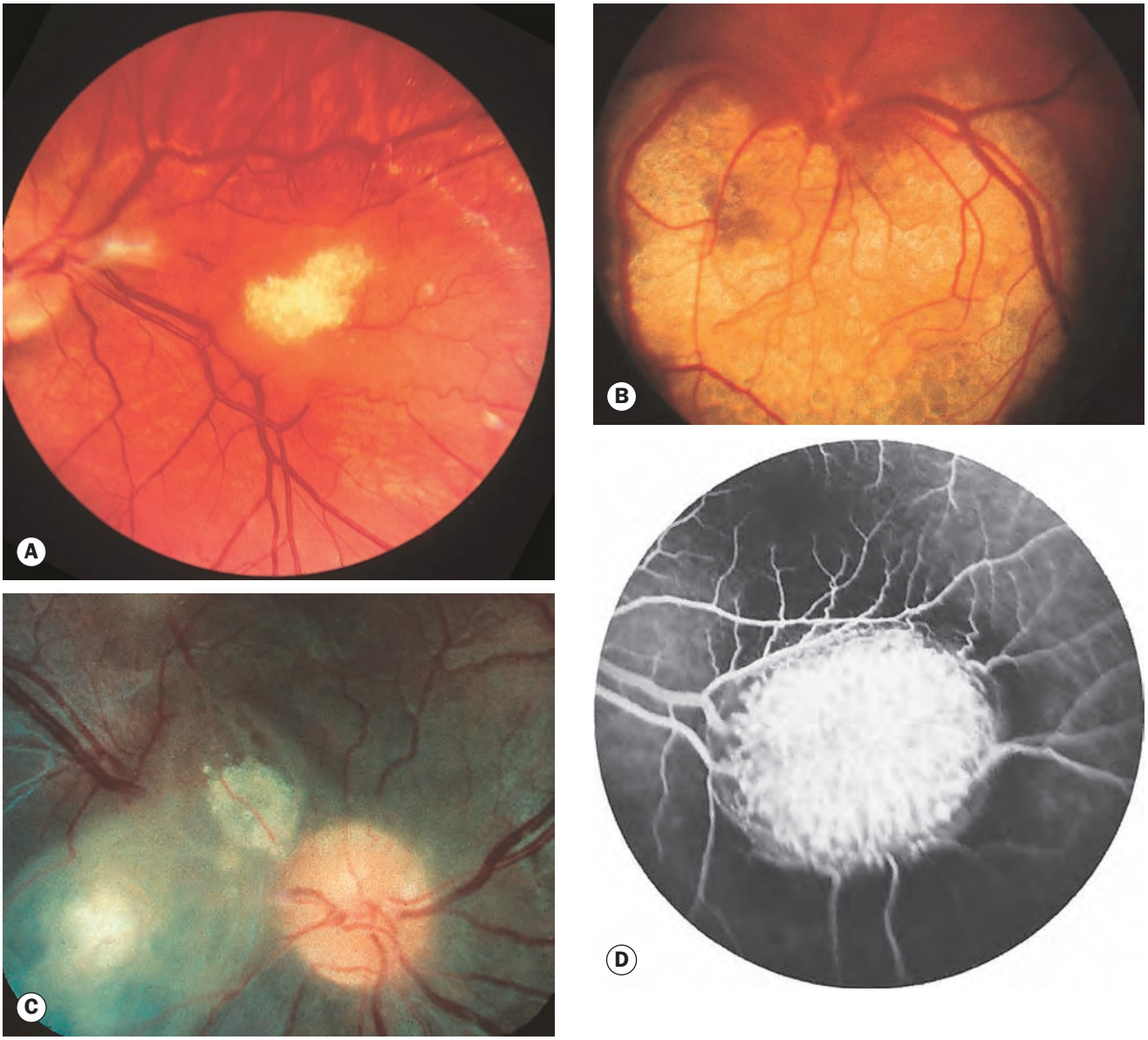


Fig. 12.45 Astrocytoma. **(A)** Yellowish mulberry-like lesion; **(B)** large diffuse lesion; **(C)** cystic variant; **(D)** FA showing staining *(J Donald M Gass, from* Stereoscopic Atlas of Macular Diseases, *Mosby 1997 – fig. D)*

- **FAF** findings depend on the individual lesion's characteristics; typically hyperautofluorescence is seen in calcified areas with hypoautofluorescence elsewhere.
- **FA** shows a prominent superficial vascular network within the tumour in the arterial phase followed by late leakage and staining (Fig. 12.45D).
- **Systemic assessment.** With an isolated astrocytoma discovered incidentally in an older patient, the likelihood of the presence of forme fruste tuberous sclerosis is low. However, the option of genetic testing and systemic investigation may be offered.

Tuberous sclerosis

Tuberous sclerosis (Bourneville disease) is an autosomal dominant phacomatosis characterized by the development of hamartomas in multiple organ systems from all primary germ layers. The classic triad of epilepsy, mental retardation and adenoma sebaceum is present in only a minority of patients, but is diagnostic. About 60% of cases are sporadic and 40% are autosomal dominant.

- **Cutaneous signs**
  - Adenoma sebaceum, consisting of fibroangiomatous red papules with a butterfly distribution around the nose and cheeks (Fig. 12.46A), is universal.
  - Ash leaf spots are hypopigmented macules on the trunk, limbs and scalp (Fig. 12.46B). In infants with sparse skin pigmentation they are best detected using ultraviolet light, under which they fluoresce (Wood lamp).
  - Shagreen patches consist of diffuse thickening over the lumbar region.
  - Subungual hamartomas (Fig. 12.46C).
  - Skin tags (molluscum fibrosa pendulum).
  - Café-au-lait spots.
- **Neurological features**
  - Intracranial paraventricular subependymal astrocytic nodules and giant cell astrocytic hamartomas.
  - Learning difficulties.
  - Seizures.
- **Visceral tumours**
  - Renal angiomyolipomas and cysts.
  - Cardiac rhabdomyomas.
  - Pulmonary lymphangiomatosis.
- **Ocular features** apart from fundus astrocytomas include patchy iris hypopigmentation and atypical iris colobomas.

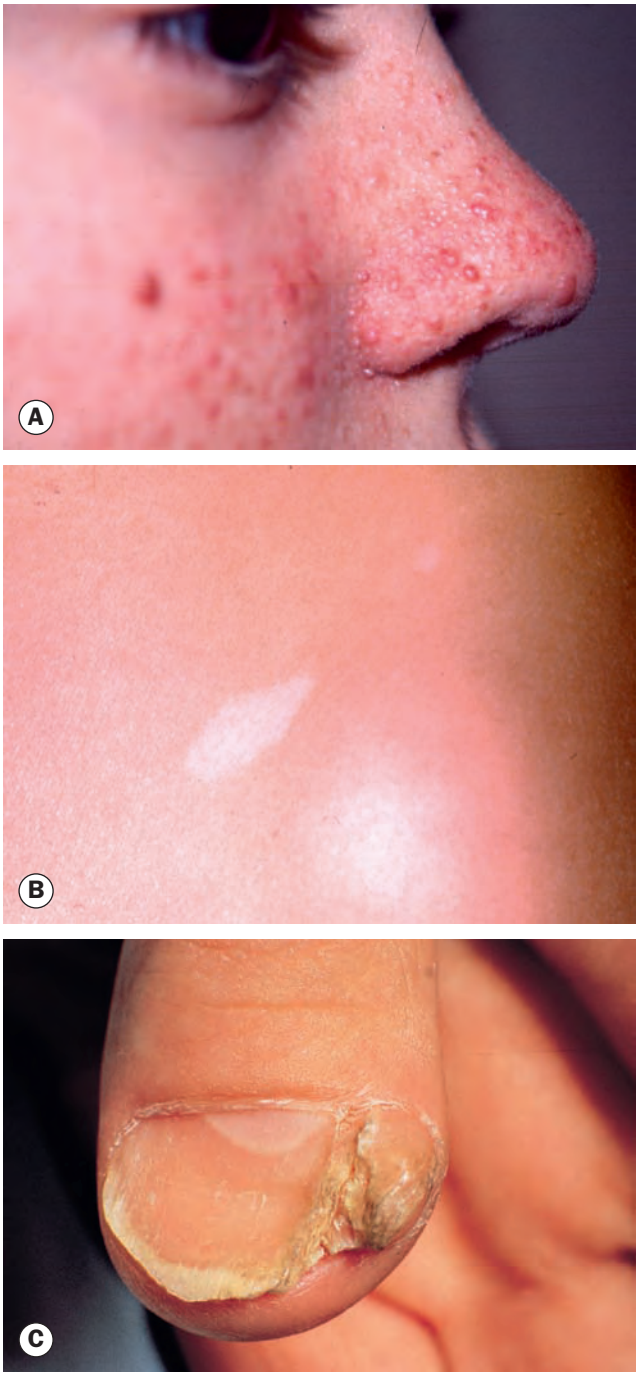


Fig. 12.46 Tuberous sclerosis. **(A)** Adenoma sebaceum; **(B)** ash leaf spot; **(C)** subungual hamartoma

(Courtesy of K Nischal – fig. A; MA Mir, from Atlas of Clinical Diagnosis, *Mosby 2003 – fig. B)*

RETINAL VASCULAR TUMOURS

Capillary haemangioma

Introduction

Retinal capillary haemangioma is a rare sight-threatening tumour that may occasionally occur in isolation, although about 50% of patients with solitary lesions and virtually all patients with multiple lesions have von Hippel–Lindau disease (VHL – see below).

The prevalence of retinal tumours in VHL is approximately 60%. Vascular endothelial growth factor (VEGF) is important in the development of retinal lesions, which are composed of capillary-like vascular channels between large foamy cells. The median age at haemangioma diagnosis in patients with VHL is earlier (18 years) than in those without VHL (31 years).

Diagnosis

- **Symptoms.** Tumours may be detected by screening of those at risk or because of symptoms due to macular exudates or retinal detachment.
- **Signs**
  - Early tumours appear as small red oval or round lesions located between an arteriole and venule (Fig. 12.47A).
  - A well-established tumour is seen as a round orange-red mass, usually located in the superior or inferior temporal periphery with dilatation and tortuosity of the supplying artery and draining vein extending from the optic disc (Fig. 12.47B).
  - A juxtapapillary site is common (Figs 12.47C and D); lesions are often on the temporal side of the disc, so that leakage can rapidly threaten the fovea.
- **Complications**
  - Leakage with exudate formation and/or haemorrhage.
  - Fibrotic bands, which can progress to tractional or rhegmatogenous retinal detachment.
  - Vitreous haemorrhage, secondary glaucoma and phthisis bulbi.
- **FA** shows early hyperfluorescence and late leakage (Figs 12.48A and B).

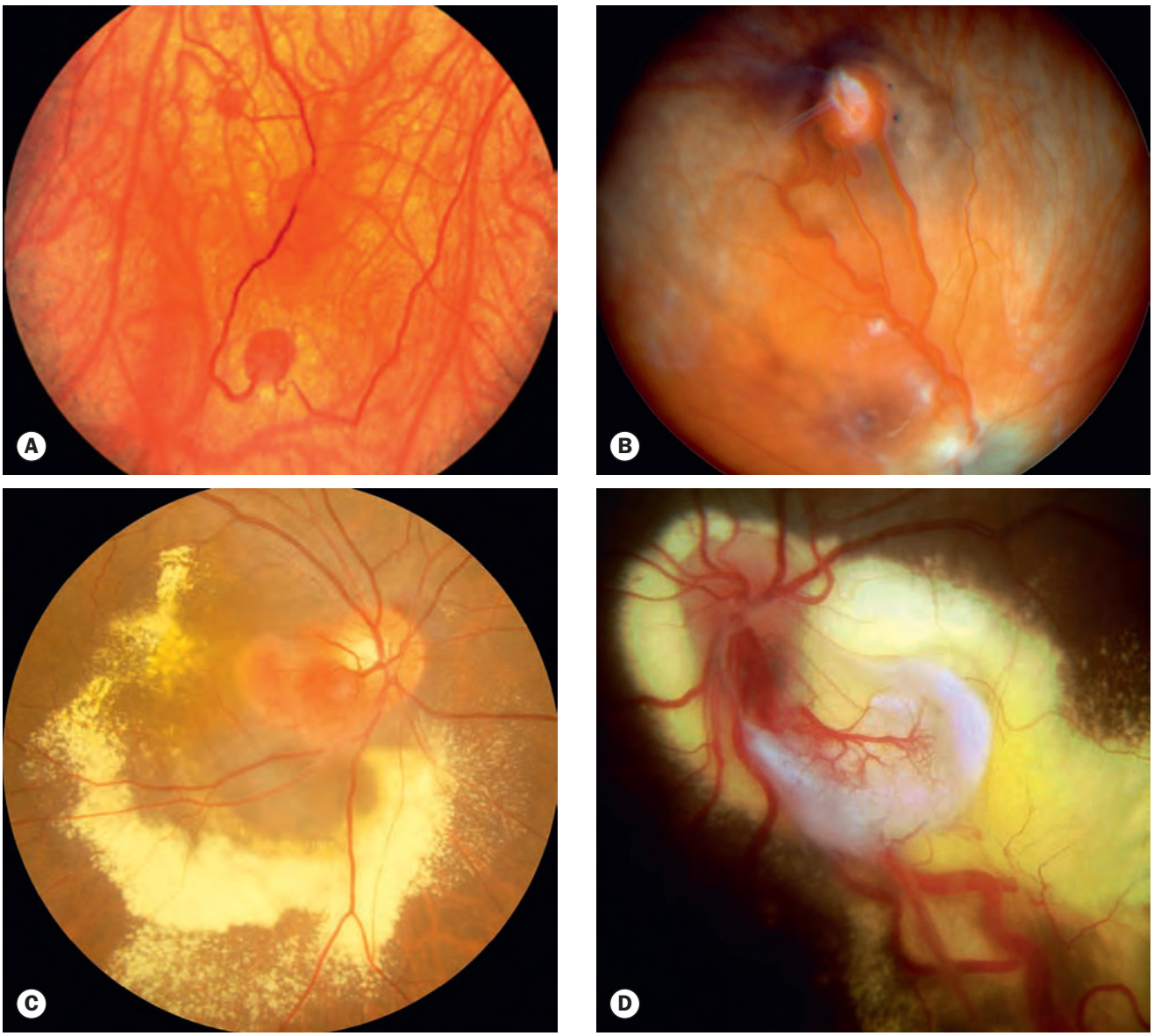


Fig. 12.47 Retinal capillary haemangioma. **(A)** Two early tumours; **(B)** more advanced lesion; **(C)** optic disc lesion with associated macular exudation; **(D)** very large optic disc lesion in von Hippel–Lindau syndrome

(Courtesy of B Damato – fig. B; C Barry – fig. C; S Chen – fig. D)

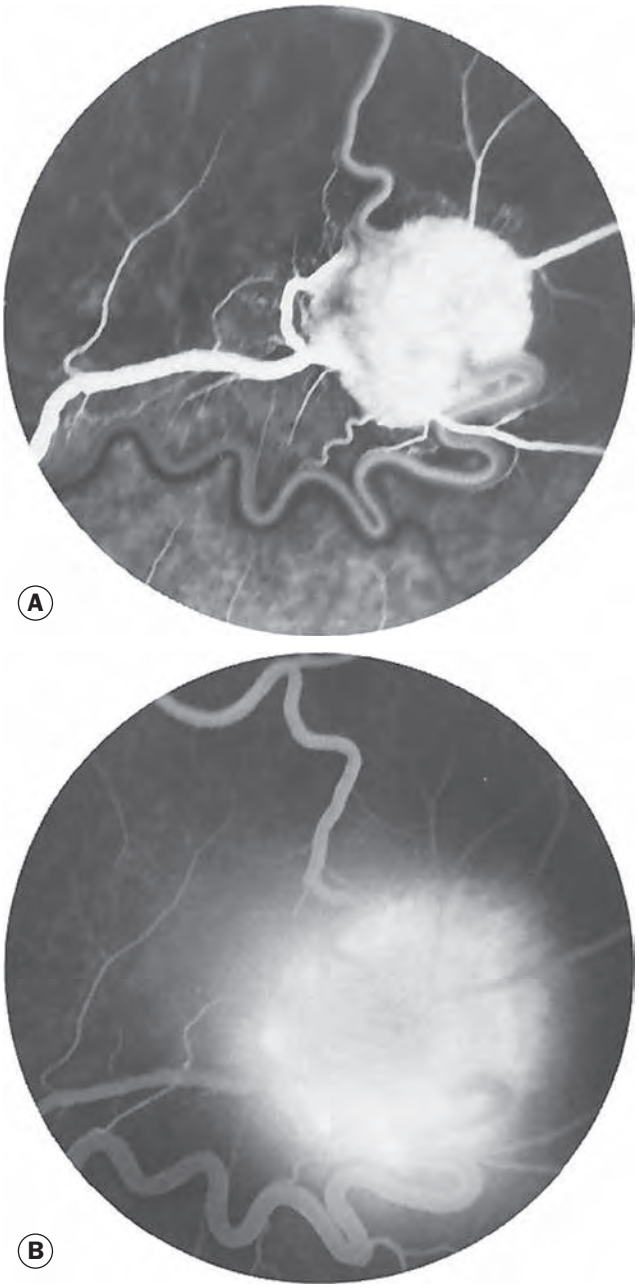


Fig. 12.48 FA of retinal capillary haemangioma. **(A)** Early filling; **(B)** late leakage

(Courtesy of J Donald M Gass, from Stereoscopic Atlas of Macular Diseases, *Mosby 1997)*

Treatment

- **Observation** is advised for asymptomatic juxtapapillary haemangiomas without exudation, because these may remain inactive for many years and because of the high risk of iatrogenic visual loss. Early peripheral lesions are not usually left untreated because they are relatively easy to ablate.
- **Laser photocoagulation** of small lesions. After closing the feeder vessels, the tumour is treated with low-energy, long duration burns. Multiple sessions may be needed.
- **Cryotherapy** for larger peripheral lesions, especially those with exudative retinal detachment. Vigorous treatment of a large lesion may cause extensive but usually temporary exudative retinal detachment.
- **Brachytherapy** for lesions too large for cryotherapy.
- **Vitreoretinal surgery** may be required for non-absorbing vitreous haemorrhage, epiretinal fibrosis or tractional retinal detachment. If appropriate, the tumour may be destroyed by endolaser photocoagulation or surgical removal.
- **Other modalities** include photodynamic therapy (PDT), which avoids damage to adjacent tissues, and anti-VEGF agents. These may be particularly appropriate for juxtapapillary tumours, which are otherwise virtually untreatable without visual loss.

Von Hippel–Lindau disease

Inherited VHL is autosomal dominant; about 20% are sporadic. It is caused by a mutation in the *VHL* tumour suppressor gene on chromosome 3.

- **Clinical features**
  - CNS haemangioma involving the cerebellum (Fig. 12.49A), spinal cord, medulla or pons affects about 25% of patients with retinal tumours.
  - Phaeochromocytoma.
  - Renal carcinoma (Fig. 12.49B) and pancreatic islet cell carcinoma.
  - Cysts of the testes, kidneys, ovaries, lungs, liver and pancreas.
  - Polycythaemia, which may be the result of factors released by a cerebellar or renal tumour.
  - Endolymphatic sac tumours develop in the inner ear in 10%, with consequent hearing and balance difficulties.
- **Screening** is vital; it is impossible to predict which patients with retinal haemangiomas will harbour systemic lesions. Relatives should also be screened because of the dominant inheritance pattern of the disease. The following screening protocol should be regularly performed in patients with established VHL and relatives at risk.
  - Annual physical examination, retinal examination from age 2 to 5 years (6-monthly from ages 10 to 30 years), renal ultrasonography from age 15 years, 24-hour urine collection for estimation of vanillyl mandelic acid and catecholamine levels from age 2 to 5 years to detect phaeochromocytoma.
  - Audiometry should be performed if there are any hearing or balance problems.
  - Two-yearly abdominal and brain MRI scans from the age of 15; if CNS lesions are symptom-free, treatment may not be required.
  - It is thought safe to discontinue screening at around age 60 years if no abnormality has been identified.
  - Genetic testing is indicated in all patients with suspected VHL and in first- and second-degree relatives. With modern techniques the likelihood of finding a mutation approaches 100%, and once a mutation has been

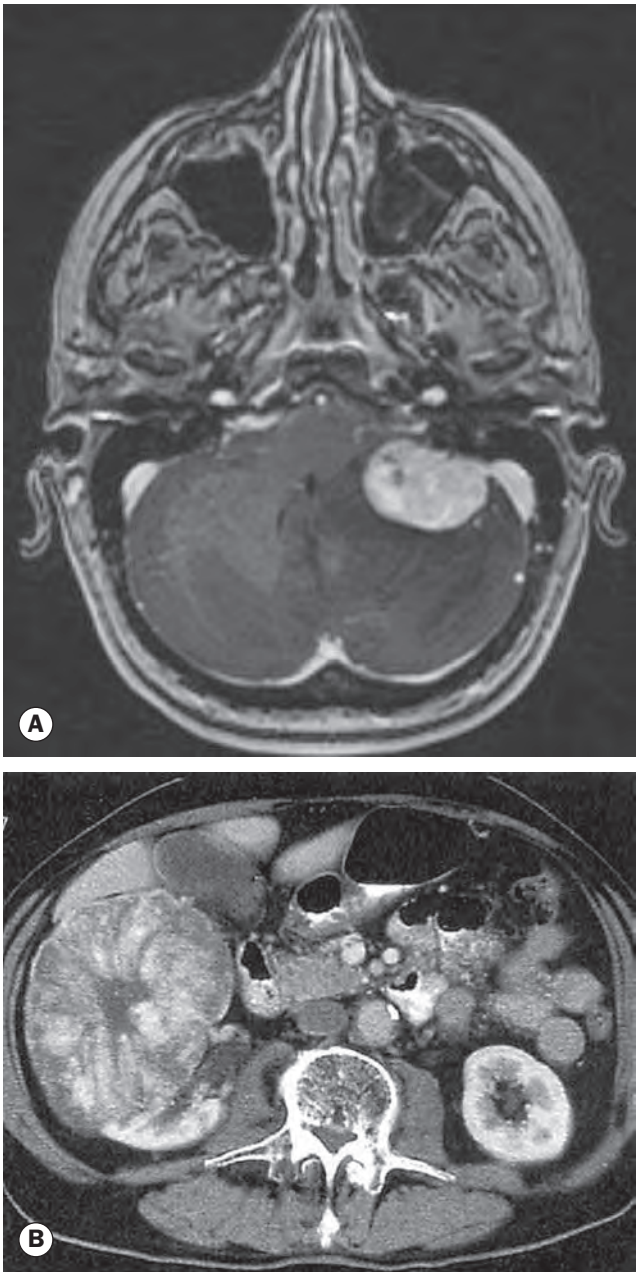


Fig. 12.49 Tumours in von Hippel–Lindau syndrome. **(A)** Axial MRI shows a cerebellar haemangioma; **(B)** axial CT of the abdomen shows a renal carcinoma

(Courtesy of CD Forbes and WF Jackson, from Atlas and Text of Clinical Medicine, *Mosby 2003 – fig. B)*

identified in the proband (initial subject) its presence can be confirmed or refuted in family members. Screening is unnecessary if the mutation is absent.

Cavernous haemangioma

Introduction

Cavernous haemangioma of the retina and optic nerve head is a rare unilateral congenital hamartoma. It is usually sporadic but occasionally can be inherited as autosomal dominant with incomplete penetrance in combination with lesions of the skin and CNS. Mutations in several different genes have been implicated. Histopathology shows multiple thin-walled dilated channels with surface gliosis.

Diagnosis

- **Symptoms** may occur secondary to vitreous haemorrhage. More frequently the lesions are detected by chance.
- **Signs**
  - Clusters of saccular aneurysms resembling a 'bunch of grapes' (Fig. 12.50A and B), with associated greyish fibrous tissue.
  - Because of sluggish flow of blood, the red cells may sediment and separate from plasma, giving rise to 'menisci' or fluid levels within the lesion.
  - A lesion occasionally involves the optic nerve head (Fig. 12.50C).
  - Haemorrhage and epiretinal membrane formation can occur.
- **OCT** demonstrates the aneurysmal vessels (Fig. 12.50D).
- **FA** highlights the sedimentation of erythrocytes and shows delayed filling in the venous phase and lack of leakage (Fig. 12.50E).

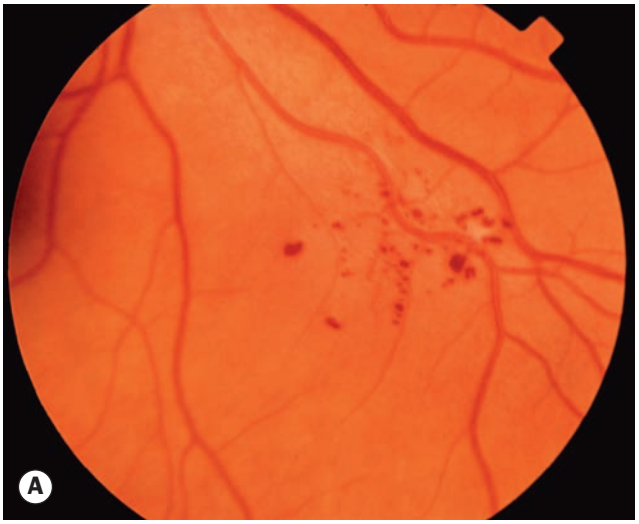
Treatment

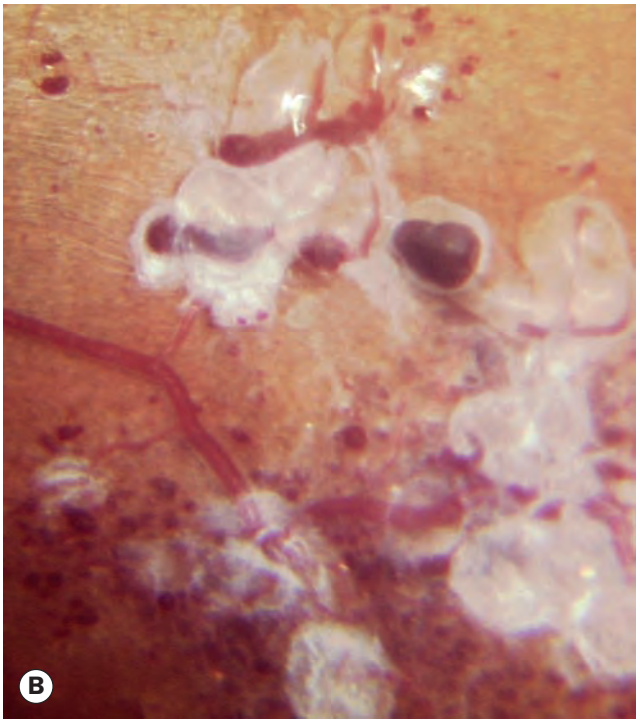
Rarely, vitrectomy may be necessary for non-absorbing vitreous haemorrhage but photocoagulation should be avoided as it may precipitate haemorrhage and enlargement of the tumour.

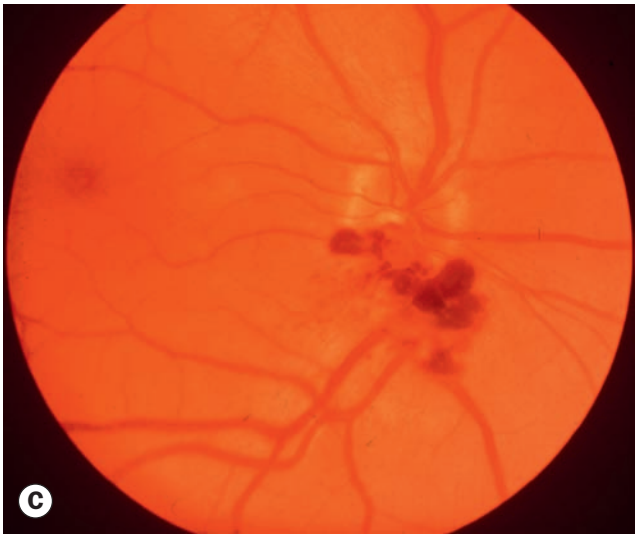
Congenital retinal arteriovenous communication (racemose haemangioma)

A congenital arteriovenous communication, the more severe forms of which are often termed racemose haemangioma, is a rare sporadic congenital malformation, with unilateral involvement in single or multiple sites of the same eye, most commonly temporally. Occasionally reported complications include haemorrhage, exudation and vascular occlusion, though the vision is commonly unaffected and the condition discovered at a routine examination. A visual field defect may be present. Some patients may harbour ipsilateral brain, facial bone and skin lesions (Wyburn-Mason syndrome), particularly those with more severe retinal changes.

- **Group 1** consists of an anastomosis with the interposition of an abnormal capillary or arteriolar plexus. A congenital retinal macrovessel is often present (Fig. 12.51A); this is an aberrant blood vessel, often larger than normal and usually a vein, located in the posterior pole; it may cross the fovea and horizontal raphe. Areas of capillary non-perfusion and foveal cysts may be seen. The anomaly is non-progressive and is usually associated with good vision.
- **Group 2.** Direct arteriovenous communication, without an intervening capillary bed. The intervening channels may be intermediate or large in size (Fig. 12.51B).







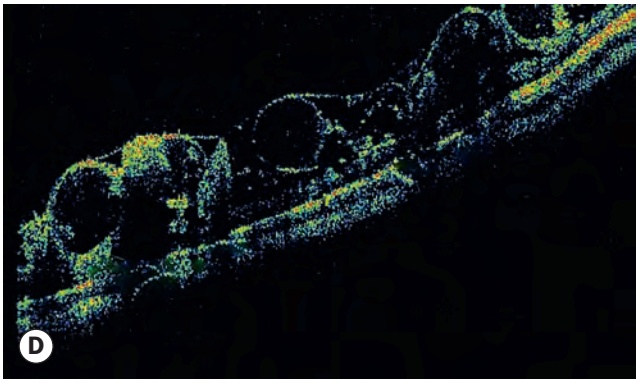


Fig. 12.50 Cavernous haemangioma. **(A)** Small peripheral lesion; **(B)** larger lesion showing fibrosis; **(C)** optic nerve involvement; **(D)** OCT of lesion in **(B)** demonstrating aneurysms; **(E)** FA shows fluid levels due to separation of red cells (hypofluorescent) from plasma (hyperfluorescent)

(Courtesy of S Chen – figs B and D; J Donald M Gass, from Stereoscopic Atlas of Macular Diseases, *Mosby 1997 – fig. E)*

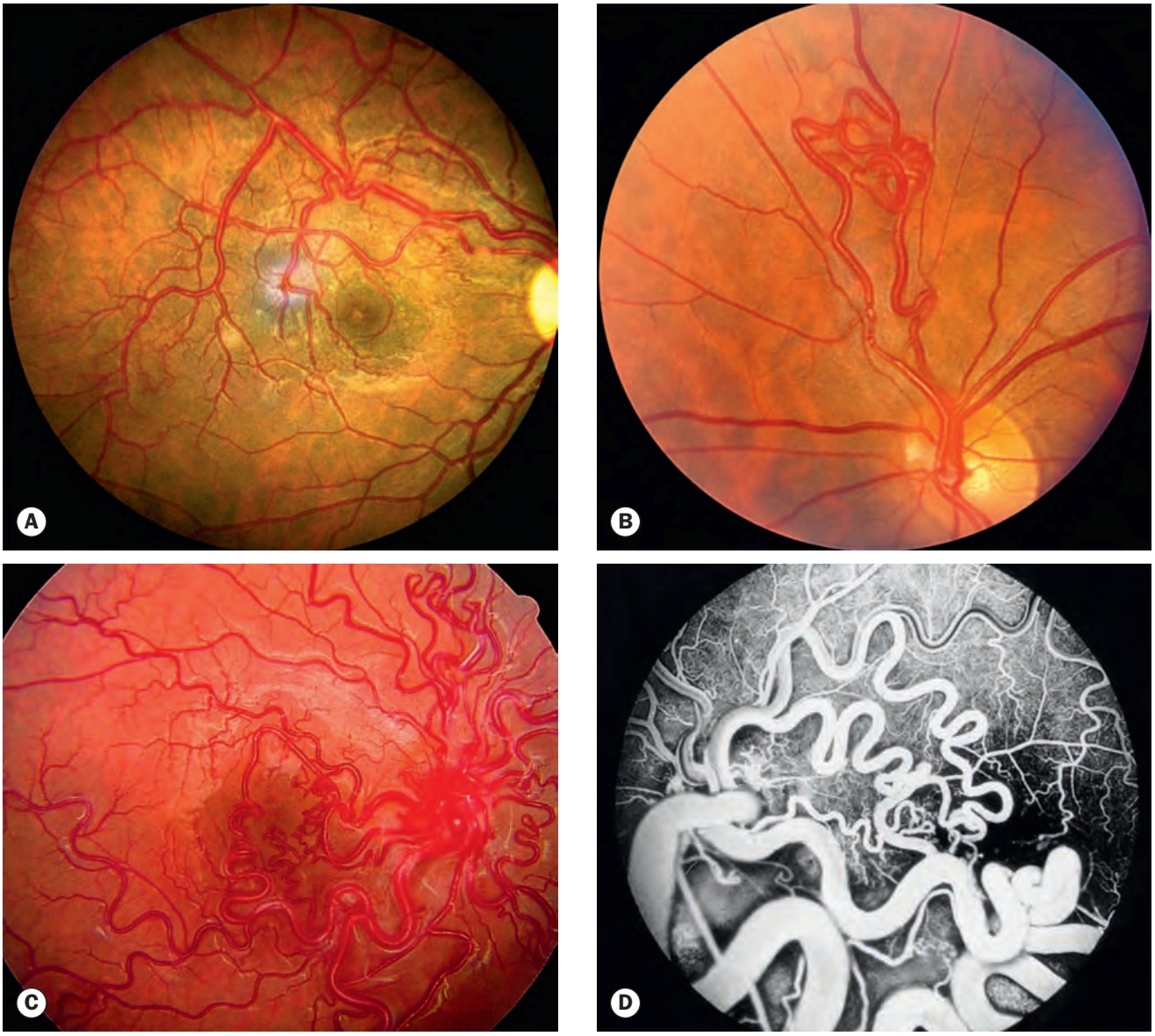


Fig. 12.51 Congenital arteriovenous communication (racemose haemangioma spectrum). **(A)** Group 1 lesion – retinal macrovessel; **(B)** group 2 – arteriovenous communication; **(C)** group 3 – typical racemose lesion with early sclerosis; **(D)** FA shows hyperfluorescence but absence of leakage

(Courtesy of C Barry – fig. B; J Donald M Gass, from Stereoscopic Atlas of Macular Diseases, *Mosby 1997 – fig. C)*

- **Group 3.** Many large-calibre tortuous anastomosing blood vessels that are often more numerous than normal, with venules and arterioles having a similar appearance. The changes extend from and are most evident in the region of the optic disc. With time the dilatation and tortuosity becomes more marked, and sclerosis may be seen (Fig. 12.51C); no leakage is seen on FA (Fig. 12.51D).

Vasoproliferative tumour

Retinal vasoproliferative tumour is a rare gliovascular lesion that can be primary (80%) or secondary to conditions such as intermediate uveitis, ocular trauma and retinitis pigmentosa. Secondary lesions may be multiple and occasionally bilateral depending on the underlying aetiology. Histology shows glial cells and a network of fine capillaries with some larger dilated vessels. Presentation is usually in the third–fifth decades, with blurring of vision due to macular exudation. A reddish-yellow globular vascular mass (Fig. 12.52A) is seen, most frequently in the inferotemporal periphery; retinal vessels may be seen entering the lesion posteriorly. Complications include subretinal exudation, exudative retinal detachment (Fig. 12.52B), macular oedema and fibrosis, and haemorrhage. Treatment with cryotherapy or brachytherapy induces regression of the tumour and exudation but the visual prognosis is guarded if there is maculopathy.

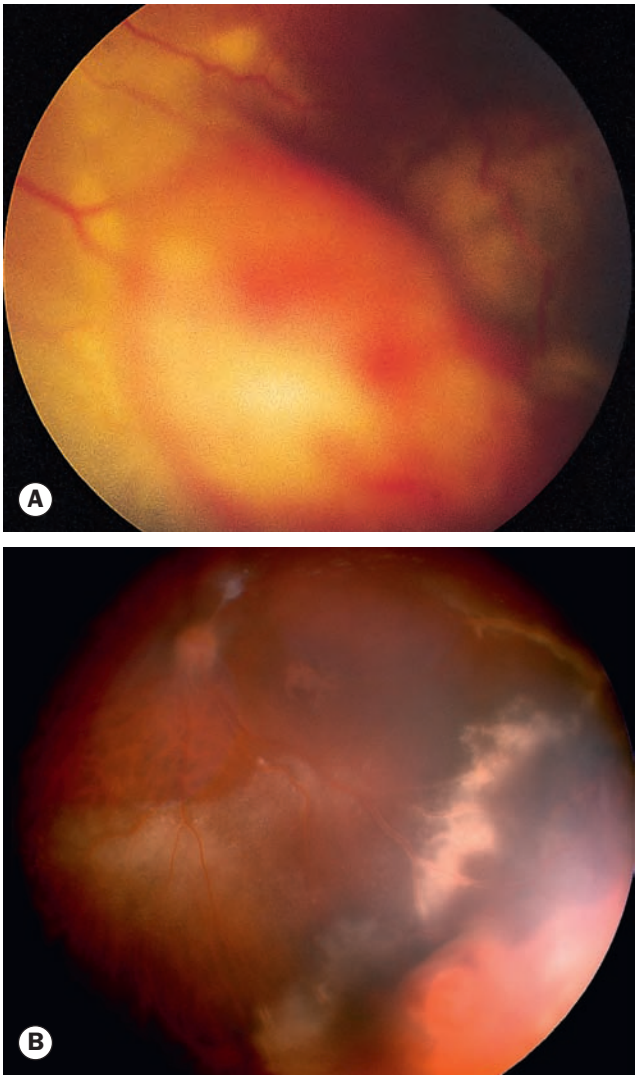


Fig. 12.52 Vasoproliferative tumour. **(A)** Globular vascular elevation; **(B)** lesion with associated retinal detachment *(Courtesy of B Damato)*

PRIMARY INTRAOCULAR LYMPHOMA

Introduction

Lymphoma is a group of conditions characterized by neoplastic proliferation of cells of the immune system typified by lymphadenopathy, constitutional symptoms and, occasionally, CNS involvement. The main classification and ocular manifestations are as follows:

- **Hodgkin disease** may cause anterior uveitis, vitritis and multifocal fundus lesions resembling chorioretinitis.
- **Non-Hodgkin lymphoma** can manifest with conjunctival involvement, orbital involvement, Mikulicz syndrome and uveal infiltration.
- **CNS B-cell lymphoma** may be associated with intermediate uveitis and sub-RPE infiltrates.
- **Primary vitreoretinal lymphoma (PVRL)** represents a subset of primary central nervous system lymphoma (PCNSL), a variant of extranodal non-Hodgkin lymphoma. The PCNSL cells are large, pleomorphic B lymphocytes with large multilobular nuclei, prominent nucleoli and scanty cytoplasm. The tumour arises from within the brain, spinal cord and leptomeninges, is aggressive and has a poor prognosis. About 20% of patients with PCNSL have ocular manifestations, which can precede or follow neurological involvement. Most patients with PVRL subsequently develop CNS symptoms, with a mean delay of 29 months. Most of those affected are older adults.
- **Primary uveal lymphoma** is a rare entity, usually of B-cell origin, that tends to follow an extended relatively benign course and will not be considered further in this section

Ocular features

- **Symptoms.** Unilateral floaters, blurred vision, red eye or photophobia. The symptoms frequently become bilateral after a variable interval.
- **Signs of PVRL**
  - Mild anterior uveitis with cells, flare and keratic precipitates.
  - Vitritis (Fig. 12.53A) may impede visualization of the fundus.
  - Large, often multifocal, subretinal infiltrates (Figs 12.53B–D).
  - Occasionally coalescence of sub-RPE deposits may completely encircle the fundus.
  - Other features include retinal vasculitis, vascular occlusion, exudative retinal detachment and optic atrophy.
  - Absence of cystoid macular oedema (CMO) is an important diagnostic indicator, since this is almost always present in true uveitic vitritis.

Neurological features

- **Symptoms.** An intracranial mass may cause headache, nausea, personality change, focal deficit or seizures; leptomeningeal disease may cause neuropathy, and spinal cord involvement may cause bilateral motor and sensory deficits.
- **Clinical neurological examination** may demonstrate abnormalities such as cranial nerve palsies, hemiparesis and ataxia.

Investigation

- **OCT** will confirm an absence of CMO in most cases, aiding differentiation from vitritis, and may demonstrate subretinal infiltrative lesions.
- **FA** shows blockage with a granular characteristic, due to the presence of sub-RPE accumulation of lymphomatous cells ('leopard skin spots').
- **US** may show vitreous debris, elevated subretinal lesions, retinal detachment and thickening of the optic nerve.

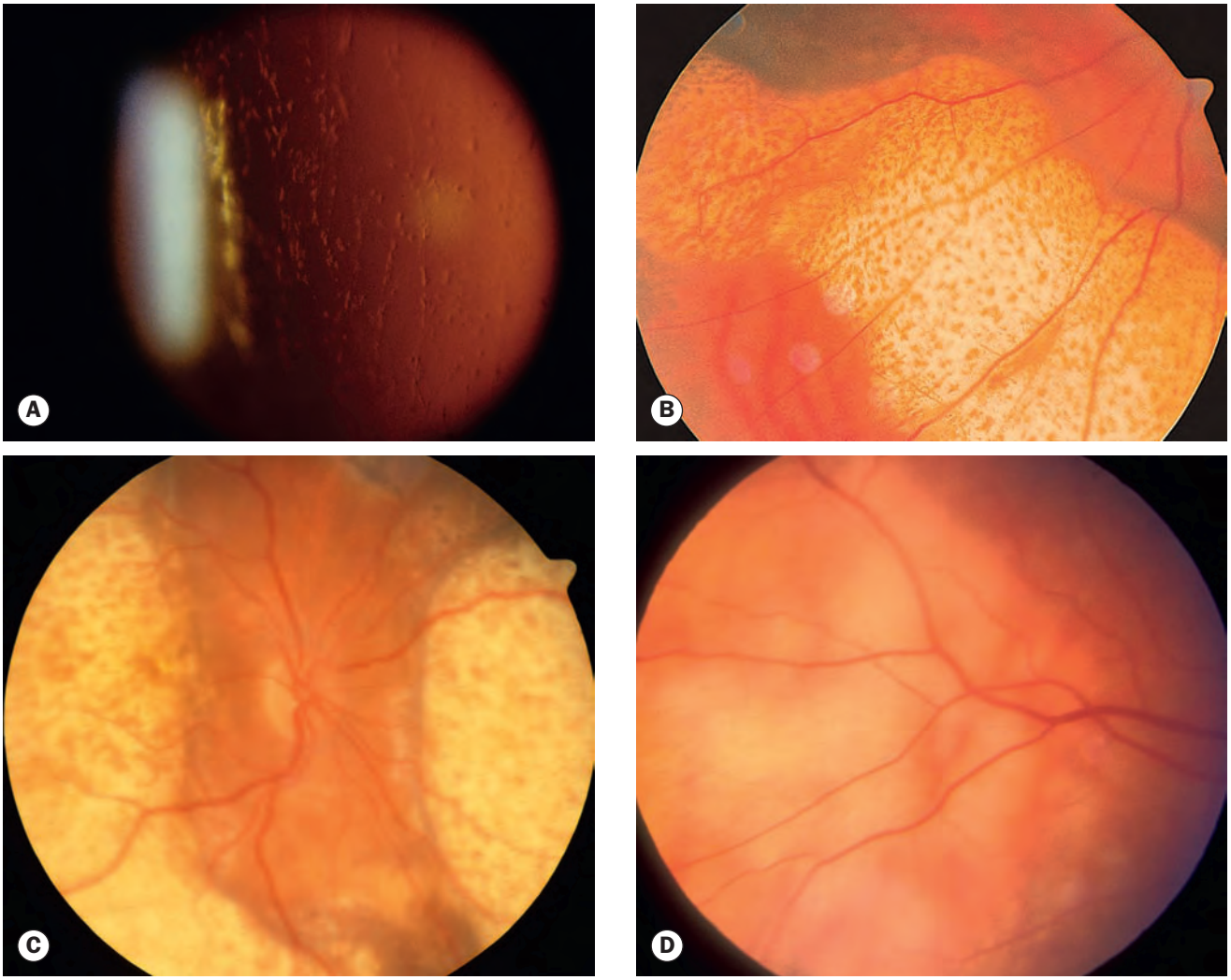


Fig. 12.53 Primary intraocular lymphoma. **(A)** Slit lamp photograph (retroillumination) showing vitreous cellular infiltrate; **(B)** and **(C)** extensive subretinal infiltration with overlying mottling; **(D)** multifocal subretinal infiltrates without mottling
(Courtesy of A Singh, H Lewis, A Schachat and D Peereboom, from Clinical Ophthalmic Oncology, *Saunders 2007 – fig. A; B Damato – fig. C)*

- **Cytology** of vitreous samples or subretinal nodules.
- **Immunohistochemistry** based on cell-surface markers allows identification of the lymphocytic proliferation, which is of a B-cell type in most patients.
- **MRI** of head and spine with gadolinium contrast may detect one or more intracranial tumours, diffuse meningeal or periventricular lesions, and/or localized intradural spinal masses; regular screening MRI scans of the CNS can be performed.
- **Lumbar puncture** may demonstrate malignant cells in the CSF in a minority of patients with abnormal MR imaging, but a positive result avoids the need for brain or eye biopsy.

Treatment

Treatment of both the eye and the brain is often indicated. Radiotherapy and chemotherapy are the mainstays, but an optimal algorithm has not been established. Treatment limited to the eye may not improve survival, but local treatment may be preferable if there is monocular disease and no evidence of involvement elsewhere.

- **Radiotherapy** has long been the first-line treatment for PVRL, but recurrence is common and complications such as radiation retinopathy and cataract can occur. It now tends to be reserved for some cases of bilateral disease but may be associated with lower recurrence rates than chemotherapy alone. It is better tolerated by younger patients.
- **Intravitreal** methotrexate is useful for recurrent disease, but close monitoring is needed to detect ocular complications and any recurrence.
- **Systemic chemotherapy** with a variety of agents such as methotrexate can prolong survival in patients with CNS disease. This can be given in combination with whole brain irradiation but neurotoxicity is a problem. A variety of methods have been developed to overcome the blood–brain barrier. Systemic treatment is usually effective for ocular

disease and this is preferred to ocular radiotherapy in some centres because in addition to avoiding radiation-induced complications it may improve survival. Monotherapy for primary intraocular lymphoma (PIOL) with ifosfamide or trofosfamide has also been successful.

- **Biologic agents involving** specific anti-B cell monoclonal antibodies (e.g. rituximab), may represent a useful alternative, but are generally given intravitreally because of poor penetration through the blood–brain barrier.

TUMOURS OF THE RETINAL PIGMENT EPITHELIUM

Congenital hypertrophy of the RPE

Introduction

Congenital hypertrophy of the retinal pigment epithelium (CHRPE) is an umbrella term encompassing three entities with distinct features and distinct implications.

Solitary (unifocal) CHRPE

- A flat or minimally elevated dark-grey or black (Fig. 12.54A), round, oval or larger scalloped-edged lesion with well-defined margins, usually located near the equator or in the peripheral fundus.
- A depigmented halo located just inside the margin (Fig. 12.54B), and depigmented lacunae (Fig. 12.54C) are common, particularly as a lesion matures; some lesions may become virtually totally depigmented.
- Median diameter is 4–5 mm but lesions can be much smaller or very large, especially in the far periphery (Fig. 12.54D), and may cause diagnostic difficulty unless the possibility of CHRPE is borne in mind.
- A posterior pole location is uncommon (2%).
- Histopathology shows densely packed RPE cells replete with large melanosomes – a combination of cellular hyperplasia and hypertrophy.
- Although formerly regarded as following a consistently stable course, a slight enlargement of the involved area over time is very common, and the development of a presumed adenomatous or adenocarcinomatous nodule arising within the lesion (see below) occurs in around 2%. Long-term review is therefore now advised.
- Solitary CHRPE does not have an association with increased gastrointestinal malignancy risk.

Grouped (multifocal) CHRPE

- Multiple lesions, much smaller than those of solitary CHRPE and without haloes or lacunae, orientated in a pattern simulating animal footprints ('bear-tracks' – Fig. 12.55A), often confined to one sector or quadrant of the fundus with the smaller spots located more centrally.
- There are typically several groups.
- Rarely the lesions may be depigmented ('polar bear tracks' – Fig. 12.55B).
- Only one eye is involved in almost all cases.
- The characteristic clinical appearance and monocular distribution serve to distinguish typical grouped CHRPE from the atypical multifocal variant associated with an increased risk of gastrointestinal malignancy (see below).

Atypical congenital hypertrophy of the RPE

- Multiple oval, spindle, comma- or fishtail-shaped lesions of very variable size associated with irregularly hypopigmented margins and perilesional areas (Figs 12.56A and B).
- Both eyes are involved.
- The lesions have a haphazard, not sectoral, distribution and may be pigmented, depigmented or heterogeneous.
- To emphasize the distinction with the CHRPE variants that are not associated with gastrointestinal malignancy, the alternative term 'retinal pigment epithelial hamartomas associated with familial adenomatous polyposis' (RPEH-FAP) has been proposed.
- **Systemic associations**
  - Familial adenomatous polyposis (FAP) is an autosomal dominant (AD) condition characterized by adenomatous polyps throughout the rectum and colon, which usually start to develop in adolescence. It results from a germline mutation in the gene *APC*; mutations falling within a certain codon range in this gene are associated with the presence of related CHRPE. Patients undergo regular colonoscopic screening with polyp excision. If untreated, virtually all patients with FAP develop carcinoma of the colorectal region by the age of 50 years. As a result of the dominant inheritance pattern, genetic testing and intensive survey of at-risk family members is imperative. Between 70 and 80% of patients with FAP have atypical CHRPE lesions, which are present at birth.
  - Gardner syndrome is characterized by FAP, osteomas of the skull, mandible and long bones, and cutaneous soft tissue tumours such as epidermoid cysts, lipomas and fibromas.
  - Turcot syndrome is an AD or autosomal recessive condition characterized by FAP and tumours of the CNS, particularly medulloblastoma and glioma.

Combined hamartoma of the retina and RPE

Introduction

Combined hamartoma of the retina and RPE is a rare lesion that is probably congenital. It may be more common in males. It typically occurs sporadically in normal individuals but sometimes in association with a systemic disorder, particularly neurofibromatosis type 2, which should be considered particularly in children or if bilateral lesions are present. Histopathology shows thickening

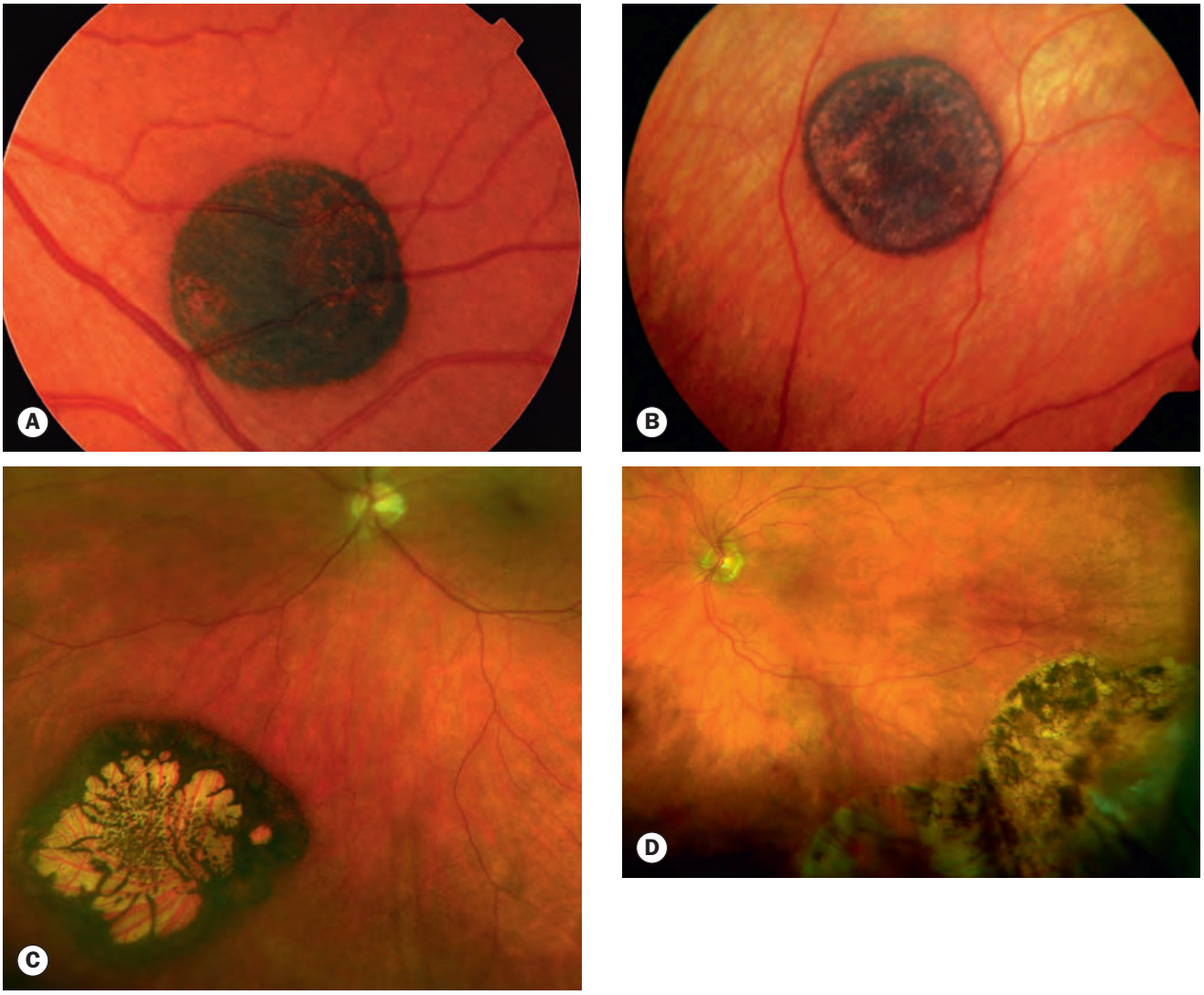


Fig. 12.54 Solitary CHRPE. **(A)** Heavily pigmented lesion; **(B)** partially depigmented lesion with halo; **(C)** large lesion with depigmented lacunae; **(D)** very large peripheral involvement
(Courtesy of S Chen – figs B and C)

of the RPE and sensory retina with prominent glial and vascular tissue.

Diagnosis

- **Symptoms.** The most common presentation is with decreased vision or strabismus in early childhood, though symptom onset in late childhood or early adulthood is also frequent.
- **VA** is 6/60 or worse in 40–50%, usually secondary to macular involvement.
- **Fundus**
  - Slightly elevated deep grey or brown – sometimes orange, yellow or green – pigmented lesion that blends into the adjacent RPE at its margins (Fig. 12.57A).
  - Superficial whitish epiretinal membrane (ERM) formation with retinal wrinkling. Occasionally vitreoretinal interface changes are marked (Fig. 12.57B), sometimes with focal tractional retinal detachment.
  - Tortuosity and prominence of overlying retinal vessels; there may be evident feeder and draining vessels.
  - The lesion is usually located at the posterior pole, often in a juxtapapillary or macular site; peripheral lesions (Fig. 12.57C) are uncommon. Dragging of the disc or macula may be present.
  - Uncommon findings include secondary macular oedema, exudation (Fig. 12.57D), choroidal and preretinal neovascularization, retinoschisis and retinal detachment.
- **OCT** will demonstrate associated epiretinal membrane formation; this has variously been reported as intrinsic to or distinct from the main lesion.
- **FA** shows early hyperfluorescence of the vascular abnormalities and blockage by pigment; the late phase may show leakage.

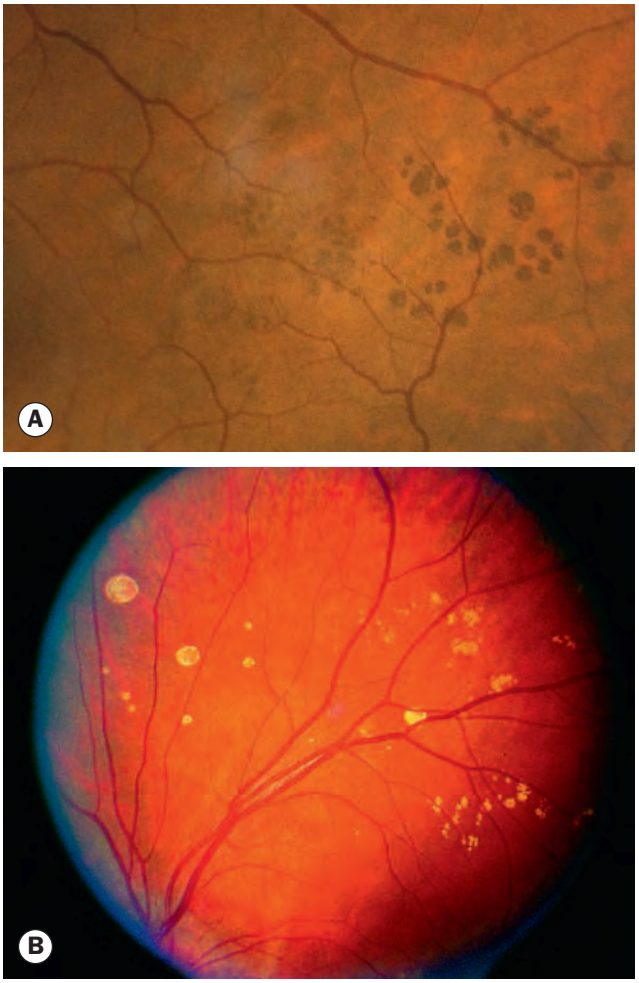


Fig. 12.55 Grouped CHRPE. **(A)** 'Bear-track' lesions; **(B)** 'polar bear track' lesions

(Courtesy of S Chen – fig. A; J Donald M Gass, from Stereoscopic Atlas of Macular Diseases, *Mosby 1997 – fig. B)*

Treatment

- **Monitoring** for complications.
- **Amblyopia therapy** is important in young children.
- **Specific treatment** for CNV and leakage where indicated.
- **Vitrectomy** for ERM has provided benefit in some cases.

Congenital simple hamartoma of the RPE

Congenital simple hamartoma of the RPE is a rare entity, usually incidentally diagnosed in asymptomatic children and young adults. It is typically a small (1.5 mm or less) jet-black nodular lesion, with well-defined margins, that appears to involve the full thickness of the retina and RPE and to protrude into the vitreous cavity (Fig. 12.58). A feeding artery and draining vein are generally seen. The lesion is typically located immediately adjacent to the foveola. VA is usually normal, but is occasionally impaired as a result of central foveal involvement or traction.

Adenoma and adenocarcinoma of the RPE

Adenoma of the RPE is an oval pigmented lesion that most commonly arises in the peripheral fundus, sometimes from an area of solitary CHRPE. Associated vitreous inflammatory cells and retinal exudation are frequently present. Associated prominent feeding and draining vessels may develop. The behaviour of an adenocarcinoma is thought to be similar to that of an adenoma. Most lesions are simply observed in the absence of vision-threatening complications, as metastasis has not been reported. Fine needle biopsy is sometimes required for diagnostic clarification.

Hyperplasia and migration of the RPE simulating uveal melanoma

Rare cases have been reported of massively proliferating RPE cells simulating a uveal melanoma, including by extraocular extension. True malignant tumours of the RPE are extraordinarily rare.

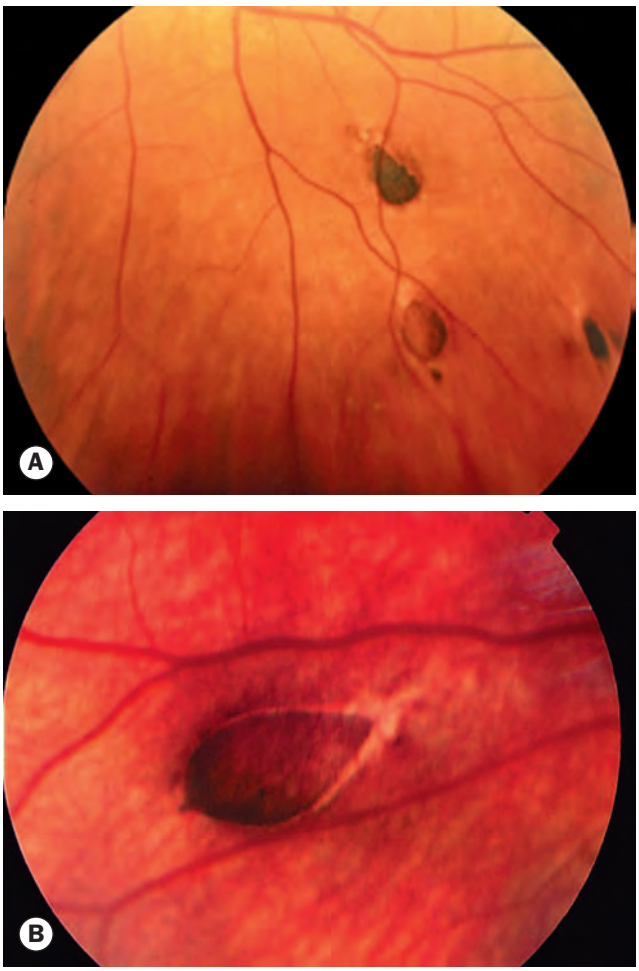


Fig. 12.56 **(A)** Atypical CHRPE; **(B)** characteristic depigmentation at one margin

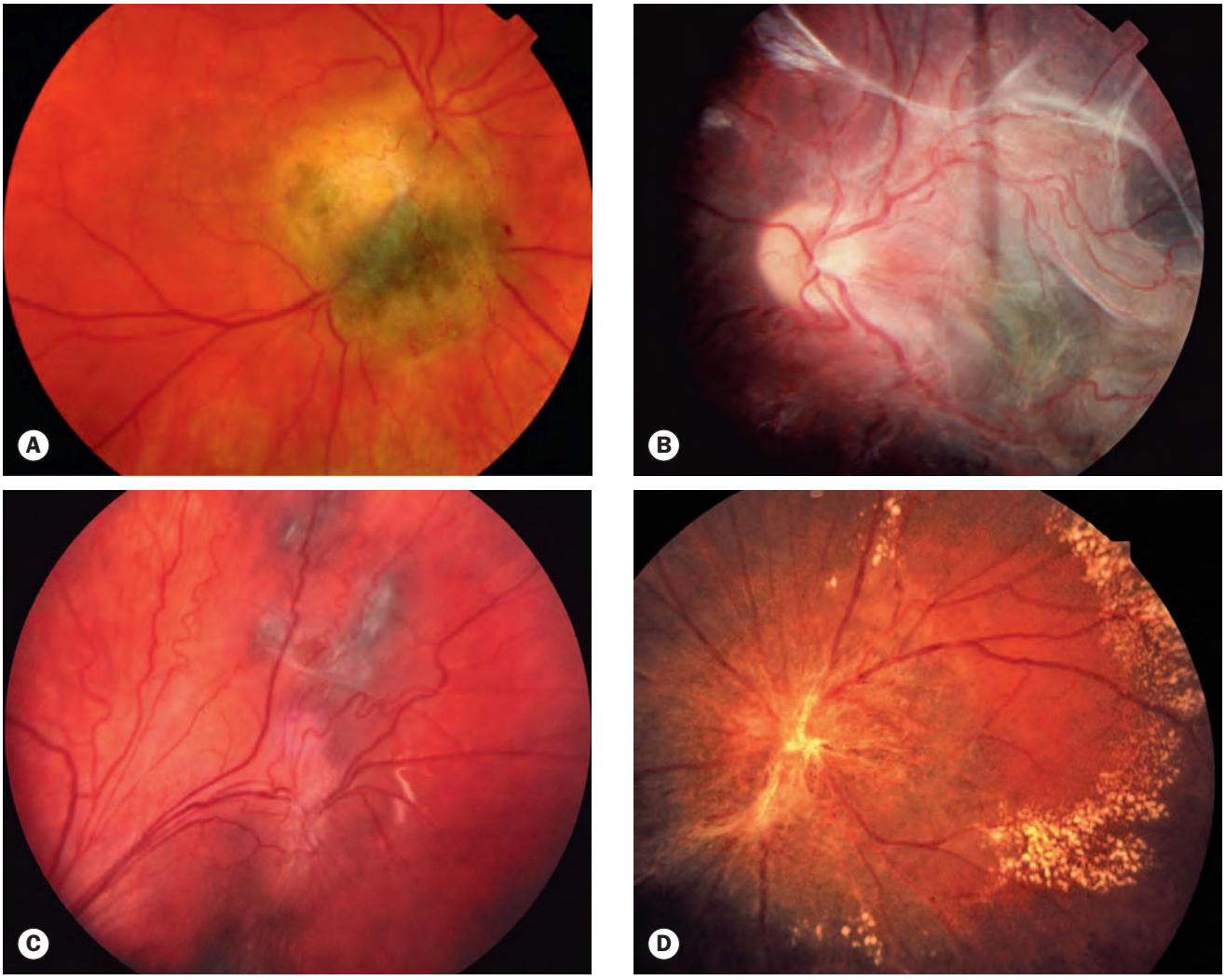


Fig. 12.57 Combined hamartoma of the retina and retinal pigment epithelium. **(A)** lesion obscuring the optic disc; **(B)** lesion with substantial preretinal glial component; **(C)** peripheral lesion; **(D)** larger peripapillary lesion with peripheral hard exudates

(Courtesy of S Chen – fig. A; S Milewski – fig. B)

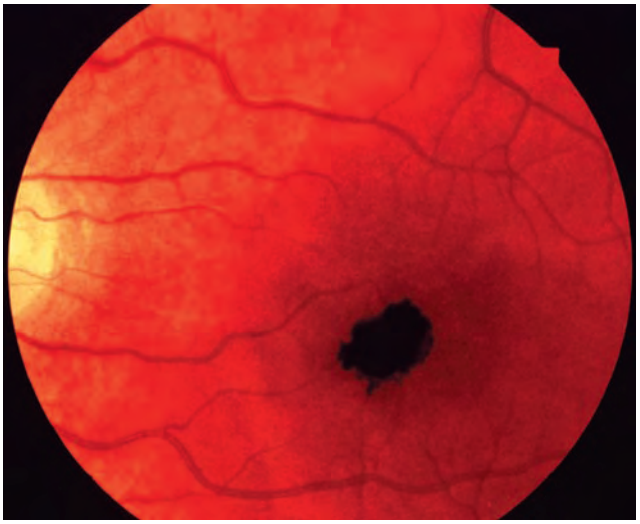


Fig. 12.58 Congenital simple hamartoma of the retinal pigment epithelium

PARANEOPLASTIC SYNDROMES

Paraneoplastic retinopathies are rare diseases that might be missed or misdiagnosed by the unwary observer. Many of the patients present with visual symptoms before the primary malignancy is diagnosed. It is therefore important for clinicians to be familiar with these syndromes in order to detect the underlying malignancy as early as possible.

Bilateral diffuse uveal melanocytic proliferation

Bilateral diffuse uveal melanocytic proliferation (BDUMP) is a very rare paraneoplastic syndrome occurring usually in patients with systemic, often occult, malignancy. It is characterized by the proliferation of benign melanocytes in the outer choroid often manifesting with multiple naevus-like choroidal lesions (Fig. 12.59), but a variety of other anterior and posterior ocular segment

Fig. 12.59 Naevus-like lesions in diffuse uveal melanocytic proliferation
(Courtesy of A Leys)

features have been reported, including red-grey subretinal patches, rapid-onset cataract, episcleral and conjunctival lesions. Vision can be severely diminished. The mechanism is uncertain, but a circulating factor may be responsible in many cases. Detection of an occult primary malignancy might enable early treatment to enhance survival. Treatment of BDUMP itself is generally unrewarding – improvement with plasmapheresis has been reported – although successful treatment of the underlying primary tumour may be followed by regression of the BDUMP, but without improvement in vision.

Cancer-associated retinopathy

Cancer-associated retinopathy (CAR) is most frequently associated with small cell bronchial carcinoma. Visual symptoms precede the diagnosis of malignancy in half the cases, typically by several months but sometimes several years. Subacute visual loss occurs over weeks to months associated with photopsia; colour impairment, glare, photosensitivity and central scotoma are attributed to cone dysfunction. Night blindness, impaired dark adaptation, ring scotoma and peripheral field loss occur due to rod dysfunction. The fundus often appears normal on presentation, but attenuated arterioles, optic disc pallor and mild RPE changes develop as the disease progresses. The electroretinogram (ERG) is abnormal at an early stage under both photopic and scotopic conditions. As with BDUMP, CAR should prompt a thorough search for an underlying malignancy, though this is not always found and the condition is then regarded as an autoimmune retinopathy.

Melanoma-associated retinopathy

The presentation of melanoma-associated retinopathy (MAR) differs from CAR in that the visual symptoms usually arise after, rather than prior to, the diagnosis of cutaneous melanoma. There may be concurrent vitiligo. Autoantibodies from MAR sera react against bipolar cells in human retina; clinical and electrophysiological data also implicate bipolar cells as the target in MAR. Generally, symptoms and signs are less marked than in CAR. The ERG shows marked reduction of dark-adapted and light-adapted b-wave and preservation of a-wave (normal photoreceptor function), characteristic of bipolar cell dysfunction. The prognosis for vision is typically good.